

Using electronic methods of
adherence monitoring and
therapeutic drug monitoring (TDM)
to eliminate discordance between
antiretroviral adherence and
virological failure.

by

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Declaration page.

I, Catherine Orrell, hereby declare that the work on this thesis is based on my original work and that neither the whole work or any part of it has been, or is being, submitted for another degree in this or any other university. In the case of multi-authored published papers, this constitutes work for which I was the lead author. My contribution to multi-authored papers is outlined in the preface to the thesis.

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List of abbreviations.

ART: Antiretroviral therapy

AZT: Zidovudine

CDC: Centre for Disease Control

DOT: Directly observed therapy

DTHC: Desmond Tutu HIV Centre

EDCTP: European and Developing Countries Clinical Trial Partnership

EFV: Efavirenz

HCTC: Hannan Crusaid Treatment Centre, Gugulethu

HIV: Human Immunodeficiency Virus

IAPAC: International Association of Physicians in AIDS Care

iDART: Intelligent Dispensing of AntiRetroviral Therapy

IeDEA-SA: International Epidemiologic Databases to Evaluate AIDS –Southern Africa

IC: Inhibitory concentration

LPV/r: Lopinavir/ritonavir

MEMS: Medical Electronic Monitoring System

NHLS: National Health Laboratory Service

NRTI: Nucleoside reverse transcriptase inhibitor

NNRTI: Non-nucleoside reverse transcriptase inhibitor

NVP: Nevirapine

PK: Pharmacokinetic

PR: Pharmacy refill

RCT: Randomised Controlled Trial

SoC: Standard of care

SR: Self-report

TAP study: A randomised controlled Trial to explore Adherence-failure relationships in a South African antiretroviral delivery site using an electronic adherence device and sparse Pharmacokinetic sampling

TDF: Tenofovir

TDM: Therapeutic Drug Monitoring

TR: Tablet returns

VL: Viral load

WHO: World Health Organisation

Preface.

This thesis includes a number of published papers in lieu of the results chapters, as per general provision 6.7 in the General Rules for the Degree of Doctor of Philosophy (PhD) of the University of Cape Town. This has been done with the approval of the 2015 University Doctoral Degrees Board. My supervisors were Professors Robin Wood, and Gary Maartens, both affiliated to the Department of Medicine, University of Cape Town.

The following four papers are included as part of the thesis. I can confirm that all authors are aware that these manuscripts were also part of a PhD and have agreed to their use for this purpose. The role of each author is listed under the title:

1. Orrell C, Cohen K, Mauff K, Bangsberg DR, Maartens G, Wood R. A randomised controlled trial of real-time electronic adherence monitoring with text message dosing reminders in people starting first-line antiretroviral therapy.

J Acquir Immune Defic Syndr. 2015 Jul 24.

Catherine Orrell was lead investigator. She conceptualised and designed the study, and was responsible for study execution, including managing data collection. She collated, cleaned and merged all data, designed the data analyses and was involved in conducting all data analyses. She interpreted the data and wrote the first and all other drafts of the manuscript. Karen Cohen collaborated in the design of the study, discussions around data analysis plans, data interpretation and critically reviewed the manuscript.

Katya Mauff was the statistician who approved all data cleaning, supervised the data analysis, assisted in data interpretation and critically reviewed the manuscript.

David Bangsberg collaborated in the design of the study, discussions around data analysis plans, and critically reviewed the manuscript.

Gary Maartens co-supervised the study, including collaboration in the study design, discussions around data analysis and interpretation and critically reviewed the manuscript.

Robin Wood helped design the study, supervised the study, the data analysis, data interpretation and the writing of the manuscript.

2. Orrell C, Dipenaar R, Killa N, Tassie JM, Harries AD, Wood R. Simplifying HIV cohort monitoring--pharmacy stock records minimize resources necessary to determine retention in care.

J Acquir Immune Defic Syndr. 2013 Mar 1;62(3):e106-8.

Catherine Orrell was lead investigator. She conceptualised this study and executed on the design. She collated data from all sources and cleaned the data for analysis. She analysed and interpreted the data herself, and wrote all drafts of the manuscript.

Riana Dipenaar was involved on the design of the study, supported data collection and reviewed the manuscript.

Nicola Killa was involved on the design of the study, supported data collection and reviewed the manuscript.

Jean-Michel Tassie collaborated to design the study, and critically reviewed the manuscript.

Anthony Harries collaborated to design the study, and critically reviewed the manuscript.

Robin Wood helped design the study, supervised the study, the data analysis, data interpretation and the writing of the manuscript.

Chapter 5:

Orrell C, Bienczak A, Cohen K, Bangsberg DR, Wood R, Maartens G, Denti P. Effect of mid-dose efavirenz concentrations and cytochrome P450 2B6 genotyping on virological response.

International J of Antimicrobial Agents. Submitted November 2015.

Catherine Orrell was lead investigator. She conceptualised and designed the study, and was responsible for study execution, including managing data collection. She collated, cleaned and merged all data, designed and was involved in the data analyses. She interpreted the data and wrote the first and all other drafts of the manuscript.

Andrzej Bienczak helped to design the data analysis, conducted the data analysis, assisted in drafting the statistical sections of the manuscript and in data interpretation. He critically reviewed all drafts of the manuscript.

Karen Cohen collaborated in the design of the study, discussions around data analysis plans, data interpretation and critically reviewed the manuscript.

David Bansberg collaborated in the design of the study, discussions around data analysis plans, and critically reviewed the manuscript.

Robin Wood helped design the study, supervised the study, the data analysis, data interpretation and the writing of the manuscript.

Gary Maartens co-supervised the study, including collaboration in the study design, discussions around data analysis and interpretation and critically reviewed the manuscript.

Paolo Denti was involved in the design of the data analysis, supervised all data analyses and the drafting of the statistical sections of the manuscript and critically reviewed all drafts of

the manuscript.

Chapter 6:

Orrell C, Cohen K, Leisegang R, Bangsberg DR, Maartens G*, Wood R*. Comparison of six adherence measures in an ART-naïve cohort in a resource-poor setting: which best predicts virological and resistance outcomes? (*these authors contributed equally)

Journal of the International AIDS Society. Submitted November 2015.

Catherine Orrell was lead investigator. She conceptualised and designed the study, and was responsible for study execution, including managing data collection. She collated, cleaned and merged all data, designed the data analyses and conducted all data analyses herself. She interpreted the data and wrote the first and all other drafts of the manuscript.

Karen Cohen collaborated in the design of the study, discussions around data analysis plans, data interpretation and critically reviewed the manuscript.

Rory Leisegang assisted in cleaning pharmacy refill data and analysis of pharmacy refill measures, assisted in data interpretation and critically reviewed the manuscript.

David Bansberg collaborated in the design of the study, discussions around data analysis plans, and critically reviewed the manuscript.

Gary Maartens co-supervised the study, including collaboration in the study design, discussions around data analysis and interpretation and critically reviewed the manuscript.

Robin Wood helped design the study, supervised the study, the data analysis, data interpretation and the writing of the manuscript.

All the work presented in this thesis is original research that has not been submitted in any format for a degree elsewhere. The candidate personally conceptualised all work in this thesis, including the design and execution of the randomised controlled trial, and conducted all of the analyses in the included papers (as outlined in the methods sections of the papers), with the support of a UCT statistical consultant or student for the more complex modelling analyses (papers 1 and 4).

The candidate drafted all versions of each manuscript and was the lead and corresponding author on all of the included papers. All co-authors critically reviewed and approved the submitted manuscripts. The senior or a senior co-author on each paper has confirmed to the University of Cape Town Doctoral Degrees Board that the included papers reflect the candidate's independent scientific work.

Abstract.

Background: Adherence to antiretroviral therapy (ART) is critical: only 70% achieve viral suppression at a year. Current adherence methodologies, with slow reaction to missed dosing, inadequately predict virological outcomes. Ideal adherence methods would be cheap, easy to use, and allow rapid response to missed doses to improve outcomes. We explored ideal adherence monitoring methodology for a large public-sector ART clinic in Cape Town.

Methods: We designed a randomised controlled study for ART-naïve individuals to determine whether text messaging after a missed dose would improve adherence recorded by an electronic adherence monitoring device (EAMD), reduce treatment interruptions or impact on virological outcome (using regression modelling). Five other measures of adherence were captured prospectively during the study: self-recall (SR), clinic-based pill count (CPC), pharmacy refill data (PR-average or PR-gaps) and efavirenz concentration. The predictive value of each adherence methodology on virological and HIV-1 resistance outcomes was compared by calculating the area under the receiver operating characteristic curve, from logistic regression models. The impact of efavirenz concentration and *CYP2B6* metaboliser genotype data on failure was examined using Cox proportion hazard modelling; and the most predictive lower limit for EFV concentration was determined. Antiretroviral cohort and pharmacy refill data were compared, using simple statistics, to determine which provided the best method of determining those retained in care.

Results: 230 participants were randomised 1:1 to control and intervention arms. Text messaging significantly reduced the number of treatment interruptions of >3 days but did not improve adherence or virological outcomes. Median (IQR) adherence at week 48 was: EAMD 86 (59-94)%, SR 100 (100-100)%, TR 100 (95-107)%; PR-average 103 (95-105)% and PR-gaps 100% (95-100). Efavirenz concentration was 2.1 (1.5-3.4)mg/L. Pharmacy refill and EAMD data best predicted virological and resistance outcomes. Pharmacy refill data was more efficient at identifying individuals continuing on ART than cohort data. Efavirenz concentrations were predictive of virological outcome, but *CYP2B6* metaboliser genotype was not. The most predictive lower threshold was 0.7mg/L.

Conclusion: Our study did not show that reminders after a missed dose improved adherence, but did show that treatment interruptions were minimised, a benefit that might have had more impact had a non-naïve population been selected. More research is needed on the use of the Wisepill in identifying those with poor adherence and initiating intervention beyond text-messaging in real time. Pharmacy refill data is underutilised: electronic dispensing systems exist at most clinics and with programmatic support could be used for adherence monitoring and programme evaluation. Low EFV concentrations can predict poor virological outcomes in a naïve population; but the currently recommended therapeutic range for EFV is too high. When directly comparing six adherence measures, EAMD and pharmacy refill best predicted clinical outcomes and programmatic use of these methods should be explored.

1. Introduction.

1.1. Background - placing the importance of adherence to ART in context.

Adherence definition and nomenclature.

The human immunodeficiency virus (HIV) is a sexually transmitted virus which results in a chronic progressive illness. The HIV causes damage through inflammation and progressive decline in the CD4+ T lymphocytes, eventually resulting in death through the development of malignancies or opportunistic infections. Over the past two decades antiretroviral therapy (ART) has changed this almost uniformly fatal infectious disease into a manageable illness with a near normal anticipated lifespan, even in a resource-poor setting. (1, 2)

This increase in life years is contingent on a successful response to ART. (1) Taking ART requires daily or twice daily medication dosing of syrup, tablets or capsules, at regular times, for the rest of the HIV-infected individual's life. Adherence to ART, namely the correct following of such prescribed medication instructions, involves a number of processes, including initiation of the correct medication/s, at the correct dose, and at the correct time of day, and continuing this without interruption in treatment while being retained in care over the entire prescription period. (3)

Adherence nomenclature has changed over time, and remains under debate. Vrijens et al have recently suggested that the following terms are used:

- Initiation: whether people commence ART. These people are not seen in ART studies as they do not begin ART. Lack of trust in the health care system or negative beliefs relating to HIV and ART might be influential in initiation choices.
- Implementation: problems with carrying out the instructions given by the health care provider. Issues here might evolve from alcohol or drug use, depression or the inability to form a habit; and can result in missing single doses, interruptions in treatment (missing multiple sequential doses) or taking extra doses.

- Discontinuation: Many people do not persist in taking ART and discontinue treatment over time. Drug side-effects or a poor health provider relationship can increase these losses to care. (3, 4)

Where an individual is in their treatment process, either at initiation, implementing or discontinuing, will influence their needs. **While adherence is not the only factor impacting on treatment outcomes, it is one which can be altered.**(5) This thesis will largely focus on adherence implementation.

A large number of people require daily ART.

South Africa is home to the single largest number of individuals living with HIV. Recent estimates suggest that 6.2 to 6.8 million South Africans live with HIV, with prevalence of 12 to 18%, and a current incidence of 1.22% per annum. (6-8) Over 20% of reproductively active women are infected. (7) After an initial lag in response, from 2004 onwards antiretroviral treatment programmes have delivered ART to the general South African population through public sector clinics. In 2012, nearly a third of those living with HIV had accessed ART; in 2015 this may be as many as 3.1 million people. (6, 9)

Over time, the vast majority of those living with HIV will require ART to survive. At the start of 2015, the CD4 cell count required to access treatment in the public sector increased from 350 cells/mm³ to 500 cells/mm³. (10) In mid-2015, the START and TEMPRANO study results were released, recommending treatment at any CD4 count. (11, 12) While South Africa has not yet shifted its guidelines to include ART for all, it is widely anticipated that this will happen in the near future. Treatment expansion will improve the health of individual living with HIV, but it will also have impact at clinic level by increasing the numbers of individuals accessing care in the short term, adding to already congested HIV services. (11, 13) In addition, data show that those who start treatment in the earlier stages of the disease, while still benefitting clinically, are more frequently lost to follow-up. (14, 15) Thus, the intention to provide broader access to care may have an unanticipated negative effect by bringing people into care who are not yet ready to commit to lifelong ART, while being unable to provide adequate support for them.

The consequence of poor adherence is drug resistance.

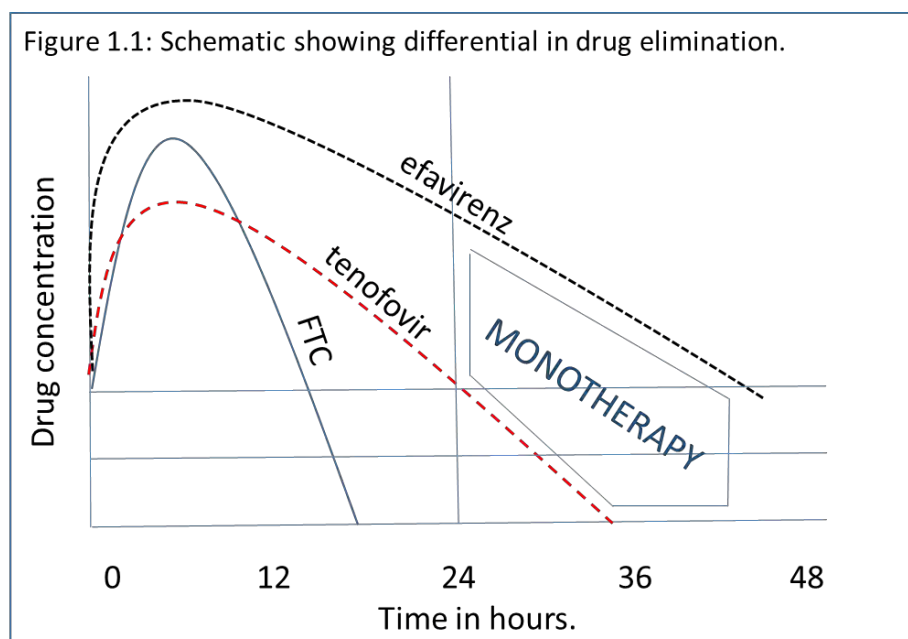
To achieve viral suppression, the concentration of each antiretroviral medication in the plasma should remain above the inhibitory concentration (IC) required to prevent 90% of the HIV (IC90) from replicating. Adequate plasma concentrations are maintained by good implementation of dosing instructions, i.e. regular daily or twice daily dosing, depending on the medication being taken.

If doses are missed, drug concentrations drop below the IC90, allowing the HIV to replicate in the presence of the medication. During replication, the viral reverse transcriptase enzyme makes errors while copying the RNA gene, with the resulting mutated virus differing structurally or functionally from the parent virus. These changes often result in development of viral resistance to an antiretroviral medication, thus giving that particular virus a survival advantage in the presence of that medication in the future.

The HIV can develop resistance to some antiretroviral medications with only a single mutation; these drugs have a low genetic barrier to resistance. This applies to all three first-line medications: tenofovir, emtricitabine and efavirenz. Other medications are more robust, with a high genetic barrier to resistance, requiring the virus to accumulate multiple mutations before the drug stops working. Combination ART, i.e. giving three medications at once, reduces the likelihood of resistance occurring.

Older ART regimens required >95% adherence, equivalent to missing fewer than three doses a month during twice a day dosing, to minimise the development of resistance. (16) Newer regimens, including medications with a longer plasma or intracellular half-life, may be more forgiving of a single missed dose, but three or more sequential missed doses, or a treatment interruption, may still result in the development of drug resistance. (17) Current first line treatment includes tenofovir, emtricitabine and efavirenz. (10) The plasma half-life ($T_{1/2}$) of tenofovir is 17 hours, emtricitabine 10 hours and that of efavirenz a much longer 52 to 76 hours. This difference in $T_{1/2}$ results in tenofovir and emtricitabine being eliminated from the plasma before efavirenz leaving efavirenz unprotected as monotherapy [Figure 1.1]. Active metabolites of some drugs, such as tenofovir diphosphate, may have

longer intracellular half-lives, rendering this picture more complex. However, missing three or more sequential doses when taking an efavirenz-containing regimen increases the risk of viral replication and the development of drug resistance.(17) This growth of resistant virus, would be followed by a reduction in CD4 cell count and progression of HIV disease despite the individual taking ART. A new regimen, often with more complex dosing, such as current second-line therapy, would then be required [Figure 1.2]. (18)



In multiple sites across sub-Saharan Africa, more than 90% of individuals who fail first-line ART have two drug class resistance, usually including resistance to lamivudine/emtricitabine and the chosen non-nucleoside reverse transcriptase inhibitor (NNRTI), either efavirenz or nevirapine.(19-22) Much of this resistance is likely to occur due to viral replication occurring in the presence of sub-optimal concentrations of ART.

In sub-Saharan Africa, viral loads are a limited resource, due to their high cost. In the South African private sector viral load monitoring is suggested every 3 to 6 months.(23) In the public sector, viral loads are only available annually.(10) In a South African public-sector cohort where viral load monitoring was more tightly monitored, HIV resistance was much less frequent and complex than seen in standard ART clinics. (19, 24) This author has shown that an intensive adherence

intervention results in 67% of those who have a first viral load >1000 copies/ml becoming re-suppressed at the subsequent viral load.(25) Tight control of adherence with early intervention thus is likely to reduce the time that virus is exposed to sub-therapeutic drug levels and thereby reduce development of drug resistance.

Not taking ART and failing to remain in care results in earlier mortality.

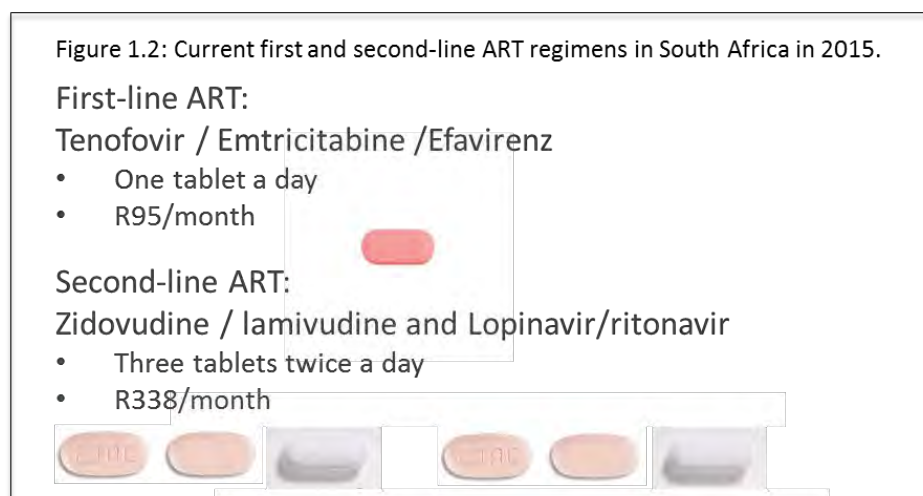
The expected lifespan of an individual with HIV is estimated to be 10 years shorter than that of someone who does not live with HIV. While the decrease in life expectancy due to HIV is greatly mitigated by the use of ART, there is still a deficit in life years due to living with the HIV. (2) In addition to this deficit, Johnson et al report a 15-20% decrease in life expectancy in individuals who fail to remain in care for 24 months. (1) Remaining in care is thus also key to reducing loss of life years due to HIV infection. Early identification of those who leave care remains a challenge.

Maintaining people on first-line ART is critical.

ART options are limited in resource-poor settings, due the public health approach required to supply large numbers of people with treatment and the cost of purchasing and delivering it. First-line ART, usually containing a NNRTI and two nucleoside reverse transcriptase inhibitors (NRTIs), is three times cheaper than second-line ART (at R95 a month vs. R338 a month). The ART in first line regimens is selected primarily due to better tolerability and low cost; despite all three drugs having a low genetic barrier to resistance. As fixed dose single tablet combinations are available for first-line ART, this regimen is easier to supply logistically, as well as to take and to adhere to, than second line treatment.(10, 26)

Current second-line ART in South Africa comprises another two NRTIs as well as a protease inhibitor. This regimen has an increased number of both tablets and dosing times, making it more difficult for an individual to maintain adherence (Figure 1.2), and for the supply chain to maintain stock. (26) Although the regimen is more robust, with a high genetic barrier to resistance, the protease inhibitor is also less well tolerated. Keeping an individual on first-line is therefore programmatically

simpler and cheaper, as well as easier and safer to take for the person involved, but lapses in adherence are more likely to result in resistance.



Current methods of monitoring adherence are inadequate.

In the early years of the expansion of ART to resource- poor settings in Africa, 2004-2007, adherence as measured by self-report, tablet returns and pharmacy refill appeared excellent in many reported cohorts, yet despite this the number of those experiencing virological failure and requiring a switch to second-line has continued to increase (27-32). Existing sub-Saharan ART programmes also have high rates of treatment discontinuation (33-35), so more recently, the impact of treatment retention and minimising treatment interruptions on virological outcomes has been explored in these populations. (17, 36-39) Many people cycle in and out of care, with each interruption increasing their risk of developing resistant HIV and thus reducing their potential years of healthy life.(37, 38)

Data from the Desmond Tutu HIV Centre (DTHC) clearly illustrates the discrepancy between adherence measures and rates of failure. This author, with other staff from the DTHC, has monitored two large antiretroviral cohorts for more than a decade. Patients taking ART at the Hannan Crusaid Treatment Centre (HCTC), a large public sector antiretroviral roll out site, in Gugulethu, Cape Town, South Africa, have been monitored since September 2002, and those at Masiphumelele clinic, South Peninsula, since 2004. Currently over 8000 individuals are being treated at both sites, with more than 1300 (16%) on second-line therapy. Over 20% of individuals

who start first-line ART at the HCTC fail first line therapy by the end of five years.
(40)

Adherence is monitored at each visit by counting the number of tablets returned unused since the previous clinic visit. A study by this author showed that adherence by tablet return was excellent ($\geq 95\%$) among those who suppressed virologically (median 97.8%). However, it was also excellent for those who failed (median 96.6%). (38) Some of those who failed did so through poor adherence ($<95\%$), but a substantial subset (19%) failed despite apparently having adequate adherence [Table 1.1].

Table 1.1: Virological outcome at week 48 by adherence category. Adherence was measured by tablet returns. (n=211).

At week 48 on first-line ART*	Viral load ≤ 50 copies/ml	Viral load >50 copies/ml
Cumulative adherence $\geq 95\%$	Expected viral suppression n=124 (59%)	<i>Unexpected non-suppression</i> n=41 (19%)
Cumulative adherence $<95\%$	Unexpected viral suppression n=28 (13%)	Expected non-suppression n=18 (7%)

*Tablet count adherence data from HCTC cohort as described by Ncaca et al. (38)

Some of the “unexpected non-suppression” may be explained by overestimation of adherence or treatment interruptions, as discussed below. “Unexpected suppression”, may be due to increased drug concentrations: in sub-Saharan Africa, genetic variants of the cytochrome p450 2B6 enzyme result in slowing of efavirenz metabolism in a proportion of the population (see Therapeutic Drug Monitoring, page 30). Higher concentrations may be more forgiving of missed ART doses.(41).

Many methods of quantifying adherence overestimate the number of doses taken. A study by this author explored different adherence measures in the paediatric cohort of the HCTC. Tablet and syrup returns overestimated adherence by 8% compared to Medical Electronic Monitoring System (MEMS) data. (42)

Interruptions or gaps in treatment may also contribute to treatment outcomes not matching adherence data. Despite excellent adherence ($>95\%$) when in possession

of ART, a single treatment interruption of 28 days or more increased the odds of failure by 5.65 (CI 1.40-22.85). (38) Other groups have noted similar losses of suppression with interruptions in treatment. (17, 39, 43) Parienti et al showed that missing more than three consecutive doses while on a NNRTI-based regimen had impact on virological outcome. Each consecutive dose missed beyond two days increased the risk of virological breakthrough.(17) Treatment interruptions in our setting are frequent and often not identified until the individual is back in care. (37, 38)

In addition, these local cohorts also experience high rates of treatment discontinuation. More than 20% of the Gugulethu cohort is considered lost to follow up by 3 years and 40% by year 7.(33, 40) Data from the National Health Laboratory Service (NHLS) indicates a 40% loss to care by 3 years in the South African ART programme (Ian Sanne, personal communication, 2015).

Current systems of monitoring patients in treatment cohorts are useful for monthly reporting and public health measures, but are often too unwieldy to be useful to most individuals. It is not helpful, in the face of adherence implementation problems, such as increased treatment interruptions and failure rates, to be using methods of monitoring adherence that are inadequate and overestimate treatment success. Similarly, it is difficult to retain individuals in care, when current systems cannot identify short treatment interruptions and only identify those lost to care more than 12 weeks after their last clinic visit. (33)

Benefits of improved adherence measurement.

While adherence is not the only factor impacting on treatment outcomes, it is one which can be altered.(5) Multiple interventions to date have been shown to improve adherence (see Literature review, page 42). Accurate and timely adherence assessments are thus critical.

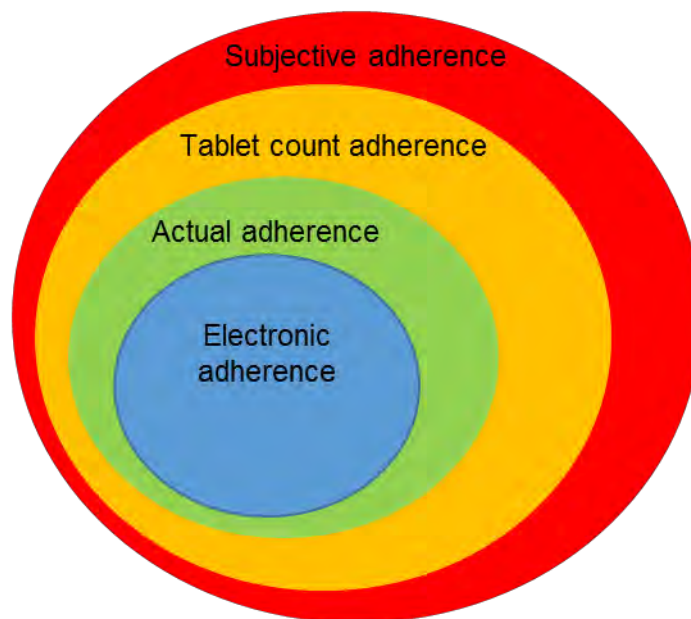
Any discontinuation begins with a few missed doses. A robust system of monitoring adherence to allow for early identification of these missed doses or treatment interruptions would allow intervention to improve adherence before viral rebound and the development of resistance. A system that could incorporate a cheap,

automated and acceptable intervention at the same time as monitoring adherence could potentially address early missed doses, without intensive staff input. Tight control of adherence with an early intervention would reduce both treatment failure and losses to care.

1.2. Methods of monitoring adherence.

If currently used methods of measuring adherence in our cohorts are inadequate, then better methods need to be identified. Since 2000 we have known that it is critical to maintain high levels of adherence in individuals being treated with HIV.(16) In the last decade, a variety of ART adherence measures have been used to determine the outcome of adherence interventions, however, to date there is still no clear gold standard for quantitating adherence [Figure 1.3]. Measures used in a clinical setting might differ from those best used for research purposes. Commonly used measures, with some advantages and disadvantages of each, are described here.

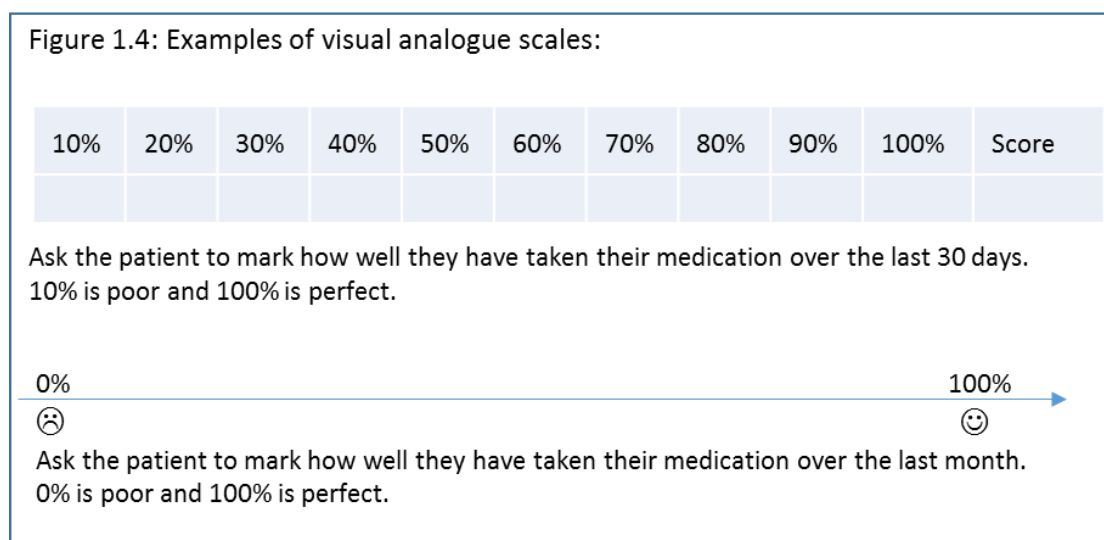
Figure 1.3. Schematic representing value of median adherence by different methods. Methods of measuring adherence may over or underestimate actual adherence.



Self report.

Self-report is a subjective measure of reporting adherence which implies that a person taking ART is asked by a clinician or an interviewer to recall the number of doses they have taken or missed over a specified period of time, usually between 3 and 30 days.(44) Shorter periods of recall, e.g. 3 days or a week, are likely to give more accurate results than longer periods.(45, 46)

Many self-reported questionnaires are based on the Adult AIDS Clinical Trials Group 3-day recall instrument where a patient is asked to remember if they took a dose that day, the day before and then day before that (a count-based measure). (47, 48) Adherence would be reported as the number of doses taken over doses possible e.g. 4 of 6 possible doses were taken (66.7%). In others estimated recall methods are used e.g. a visual analogue scale can be used for a patient to mark their estimated adherence over the specified time period [Figure 1.4].(47)



The use of self-reported adherence measures to monitor adherence is common, as these measures are easy to perform and have no added cost. (44, 49) A number of adherence studies have relied on this measure. (50-53) In most cases self-report overestimates adherence, due to recall bias and the social desire to please.(54) If asked, most people will report that they take their tablet regularly and note few missed doses. Their perception is one of good adherence, while in reality those few missed doses are significant, making this measure unreliable for research purposes.

In few cases is a subjective, self-reported adherence measure predictive of virological outcome when used alone. However, a report of incomplete adherence can be clinically useful in triggering adherence intervention. (55, 56) Prediction of virological failure is more likely when used together with an objective measure e.g. tablet return or electronic monitoring of adherence. (55, 56) Despite these limitations, recent guidelines on monitoring adherence recommend “self-reported adherence should be obtained routinely in all patients”.(5)

Tablet returns.

Tablet return is a more objective measure of ART adherence that has been commonly used. (44) In recent years the regular use of tablet returns has fallen out of favour due to the time required by clinic staff to complete the count and the complexity of the calculation required in the clinic. Tablets need to be returned, and then counted. Thereafter, adherence must be calculated based on prior dispensing dates.(38) There is again a risk of over-estimation of adherence through patients being able to deliberately modify their response e.g. altering their returns by pill-dumping so adjusting the tablets brought back to match the doses that should have been taken. (3, 5, 38, 44, 54)

A typical tablet return calculation requires four pieces of informations: a *count of the days* between the last dispensing date and the current date, knowledge of the *number of tablets dispensed* at the last dispensing date, number of *tablets taken per day* and a *count of tablets returned* at the current visit.(38)

So, percentage adherence is equal to:
$$\frac{(\text{tablets dispensed} - \text{tablets returned}) \times 100}{(\text{tablets/day} \times \text{count of days})}$$

While some studies have shown reasonable correlation of tablet return data with virological outcomes, recent comprehensive adherence guidelines suggest counts of tablet returns should not be recommended routinely.(5)

Pharmacy refill.

Data from collection of medication from the pharmacy can provide information related to continuity of ART supply. Some pharmacy refill methods simply count the number of times medication was collected over a fixed time period e.g. four out of six months; and others use dispensing dates and volume given to examine medication free days i.e. days on which the patient would have had no medication available. (57, 58)

As pick-up of medication does not guarantee actual swallowing of the tablets, and there may be more tablets in a pack than days between clinic visits e.g. 30 days of efavirenz dispensed with a 28 day next clinic date, pharmacy refill measures also overestimate adherence. The advantage of pharmacy refill measures is that all

missed or late pick-ups are noted. In common with tablet return, pharmacy refill measures do not give any information relating to timing of dosing, and also require systems in place to maintain either paper or electronic pharmacy records.(3, 54)

However, both short and longer term methods based on pharmacy refill data have been used to predict virological failure and mortality, and this method is recommended as a routine means of monitoring adherence.(57-59) Electronic dispensing systems, available in many resource- poor settings, make this method even more attractive.

Electronic devices.

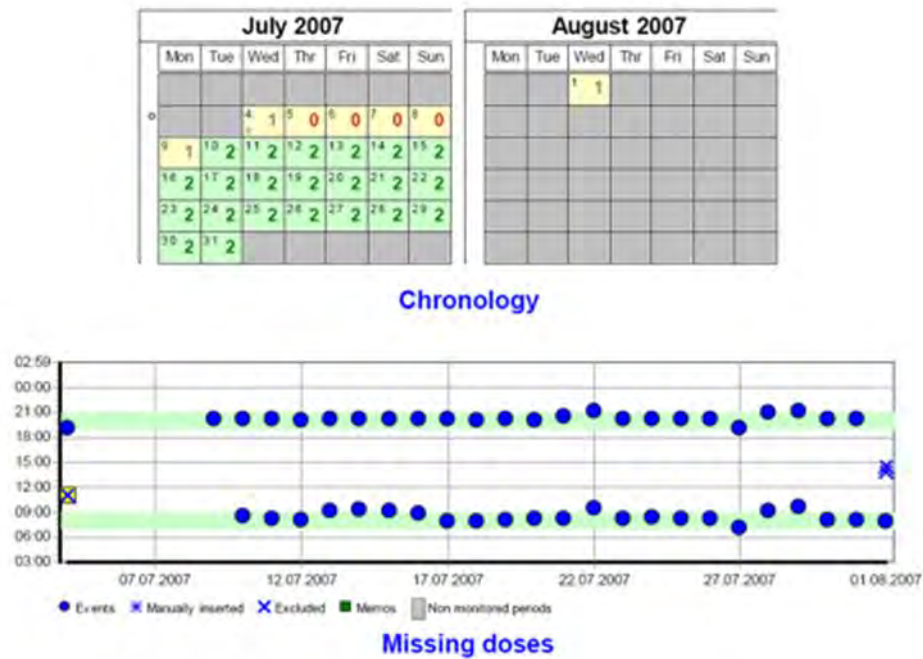
Electronic monitoring of adherence has most frequently included the use of devices such as Medication Event Monitoring System (MEMS) caps. These are lids that can be placed on a tablet or syrup bottle and which record the date of time of each opening for download at the next clinic visit [Figure 1.5].(42, 44) More recently, the Wisepill® device, an electronic pill box with a SIM card that sends a real-time signal via the cell-phone system once the box is opened has been developed in South Africa and is being used quite widely [Figure 1.5]. (60-62)

It is thought that these methods might underestimate adherence as multiple tablets can be removed from a bottle / box with only one opening, however adherence measured electronically is more consistently associated with virological outcomes than any other measure. (3, 5, 44, 54) Despite this, Thompson et al did not recommend the routine use of such monitoring as devices are expensive and often not practical to use.(5)

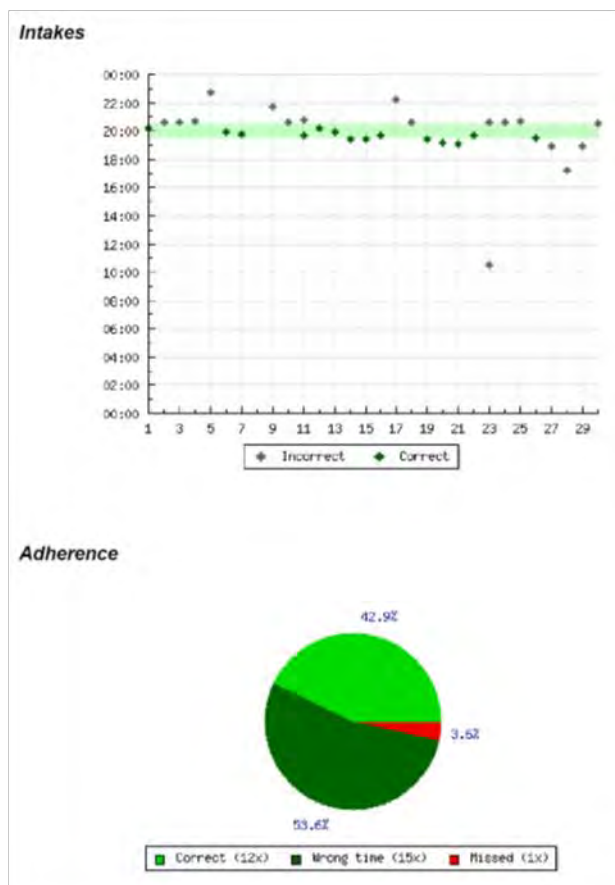
The unique advantage of using electronic monitoring over all the above measures is that the timing of the dose is also captured, allowing for the possibility of acting immediately or within a few days of missed dosing, creating real-time interventions to improve adherence.(3, 63).

Figure 1.5. a. Example of MEMS caps output and 1.3.b. Wisepill® output.

a. Dosing as recorded using a MEMS caps in children.



b. Dosing as recorded using the Wisepill® electronic pillbox.



Therapeutic drug monitoring.

Therapeutic drug monitoring is not recommended as a routine approach to measuring ART adherence (5, 64, 65), despite recent literature from HIV prevention studies showing that adherence to product is linked to concentration of drug in the blood, which is in turn linked with effectiveness.(66, 67) When using ART as treatment, reviews on the use of therapeutic drug monitoring show that therapeutic drug levels do not always correlate well with virological outcomes.(64, 65, 68) This inconsistency may be due to the lack of information on tablet-taking behaviour in many studies or possible inconsistencies between measured adherence and drug levels e.g. patients can modify outcome by dosing immediately prior to clinic visit thus having adequate drug concentration despite poor adherence. Poor adherence over time may also result in viral resistance, altering the relationship between drug concentration and viral suppression. In addition, these methods require a blood draw and laboratory capabilities.(54)

Efavirenz metabolism differs in the sub-Saharan African population. Metaboliser status (ultra-slow, slow, intermediate or rapid) due to genetic variants in the cytochrome 2B6 enzyme, results in differences in drug exposure. (41).Efavirenz metabolism is slower in a subset of this population, resulting in increased EFV levels. (69, 70) The impact of metaboliser status on the consequence of missed doses has not been fully explored: slower decline of EFV concentration might result in a more forgiving regimen, safely allowing a few doses to be missed and reducing the impact of treatment interruptions, or conversely, the higher concentrations might result in increased toxicity and lead to reduced adherence (65, 71) These genetic factors may thus also impact on the discrepancy between recorded adherence and virological outcomes.

Hair concentrations.

Measuring ART concentrations in hair is a novel method of quantitating longer-term adherence, and has been shown to be a strong predictor of virological response. (72-74) Hair levels correlate well with plasma ART levels measuring frequently used ART and reflect adherence over the duration of hair growth e.g. 4 to 6 weeks, in a similar

manner that glycated haemoglobin or HbA1C reflects longer-term glucose levels in a diabetic population.(75)

Hair samples are relatively easy to collect, store and transport. Forty to fifty hair strands from different parts of the head need to be cut off close to the scalp and stuck onto the collection form with the scalp end identified. These can be placed in an envelope and kept dry until analysis. Although, in our context, many men have shaved heads and women with braids are often reluctant to allow sampling, this non-invasive method could be a useful additional tool for predicting ART outcomes.

1.3. Problem statement and rationale for developing this thesis.

Both through review of the literature, and through taking an interest in patient adherence behaviour while working in the South African public sector ART service over the past decade, I have noted that as the ART service has expanded, so our quality of care has reduced. This is evidenced by increasing rates of virological failure and reduced retention in care, and is clearly described in a number of our publications. (14, 40, 76, 77)

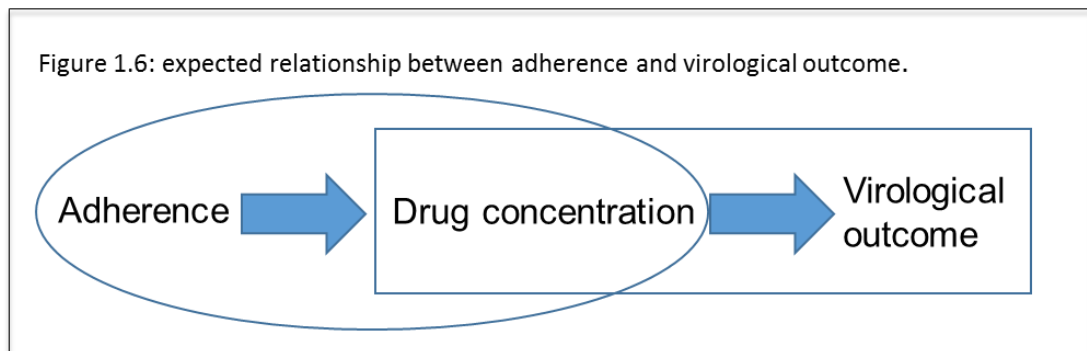
Treatment discontinuation can be thought of as a natural extension and consequence of initial poor tablet taking behaviour, either poor overall adherence execution or treatment interruptions. Losses are amplified by inadequate methods currently used to monitor individuals while they are in care, usually self-report and tablet returns, with slow or no reaction to missed dosing. Current cohort monitoring systems also do not allow immediate reaction to missed visits. Improving adherence is however time consuming and costly, usually requiring intensive intervention. (25, 78) So, at the same time as requiring more immediately reactive systems to note and act early on missed doses, there is little room within the public-sector clinic system for expansion of services either in terms of physical space or staff capacity.

An ideal adherence monitoring method for a large public-sector clinic would be cheap, easy to use, and allow rapid response to missed doses or gaps in treatment. A system which incorporated an adherence improvement intervention, immediately linked to missed doses and requiring no additional staff input would be even better.

Some questions that I hoped to answer within the studies designed for this PhD were:

- Is there a technology that could improve adherence and retention without requiring extra resources, such as staff time? Immediate or real-time monitoring might allow us to build the habit of adherence early into treatment. Eighty percent of those who have a viral load drawn at a year into ART are suppressed. Could real-time monitoring allow us to identify those more likely to fail and focus the use of expensive viral load there?

- Is it possible to maximise the use of systems that are in place already, such as the pharmacy dispensing system, which might more simply and efficiently identify those in care and those who miss visits, than current methods?
- The connection between adherence and virological outcomes should be found in drug concentrations, as noted in the HIV-prevention literature, though not in the treatment literature [Figure 1.6]. (5, 64-68)



Is this due to a lack of adherence information or less than ideal methods of estimation of adherence in these studies? Few of these studies examine EFV TDM in a resource- poor setting.(64, 65) Does the genetic difference in EFV metaboliser genotype in sub-Saharan Africans make a difference to treatment outcomes?(69, 76) Slow metabolisers with higher drug concentrations might be protected from the effect of poor adherence. Perhaps efavirenz drug concentrations can predict outcomes in a naive population, with knowledge of metaboliser status?

- Few studies directly compare adherence methodologies.(54, 61, 79) Will a comparison of multiple methods of monitoring adherence in our resource- poor setting, identify the optimal methodology?

In summary: while we can improve adherence, in order to do so, we need to be able to assess adherence as accurately as possible. The significance of poor adherence may be affected by the characteristics of the ART used and the metaboliser status of the individual. The desired outcome is to improve virological suppression and reduce development of HIV resistance to first-line antiretroviral therapy.

1.4. Objectives.

The aim of this PhD was to focus on adherence implementation, through exploring newer adherence methodologies, including electronic adherence monitoring, iDART pharmacy dispensing technology and drug concentrations, using locally available and developed resources, in order to determine which of these might improve the monitoring of adherence and either more accurately predict virological or resistance outcomes or allow more real-time reaction to missed doses or missed visits. This included the assessment of whether the use of text message reminders soon after a missed ART dose could improve adherence, reduce treatment interruptions and decrease loss to care.

We hypothesised that the use of real-time adherence monitoring would reduce the overestimation of adherence seen with other methods, including self-report, pill count, and pharmacy refill data. With the addition of a reminder sent by text message in the randomised arm should dosing be late, we hypothesised that electronic adherence monitoring would improve adherence, reduce treatment interruptions and subsequently reduce first-line ART failure rate. In addition we hypothesised that EFV drug concentrations would predict virological outcome in an ART-naïve population, with knowledge of cytochrome 2B6 metaboliser status.

More specifically the objectives of this PhD were:

1. To determine whether a locally developed real time electronic adherence monitoring device (Wisepill®) with an immediate cell phone text message feedback intervention can improve adherence, reduce treatment interruptions and increase retention in care in an ART-naïve South African population.
2. To determine whether an existing locally developed pharmacy database, Intelligent Dispensing of Antiretroviral Therapy (iDART), can be used to more accurately and rapidly monitor adherence and retention in care for local ART cohorts.

3. To determine whether knowledge of pharmacogenetic data and mid-dose efavirenz concentrations can predict treatment outcome in a sub-Saharan African population.
4. To compare multiple different methods of quantifying adherence within one cohort and to determine whether electronic adherence monitoring using Wisepill® better predicts virological and resistance outcomes than standard adherence measures, including self-report, tablet returns, iDART pharmacy refill data and spot EFV concentrations.

1.5. Data sources.

Observational data

The Desmond Tutu HIV Foundation (DTHF) has been involved in monitoring and evaluation of two large community antiretroviral services since 2002. The two clinics are Masiphumelele in the South Peninsula and the Hannan Crusaid Treatment Centre (HCTC) in Gugulethu. Over 14 000 patients have entered care at these two sites over the last 13 years. As of May 2015, over 8000 remain in care. Both cohorts are managed according to the South African National ART Guidelines and have been well described in the literature. (25, 37, 40, 80, 81). Both sites donate data annually to the leDEA-Southern Africa collaboration.(82, 83)

At entry, the demographics and clinical status of each patient is recorded: date of birth, gender, WHO clinical stage, baseline CD4 cell count and viral load (where available).

All ART drug dispensing data is captured from the electronic pharmacy dispensing system at both sites (iDART). From 2007 iDART data was downloaded directly into the HCTC database, and from the end of 2012 was incorporated into the Masiphumelele database. iDART was developed locally by Professor Robin Wood and Cell-Life (UCT Department of Engineering). (84)

Laboratory data, including viral load and CD4 cell count results, from the National Health Laboratory Service (NHLS), are downloaded into both databases monthly.

Tablet returns are counted at each clinic visit and an adherence percentage calculated and recorded in the folder.

All patients who are more than a month late for a clinic visit (i.e. 12 weeks since their last visit to clinic, blood draw or collection of ART) are traced and an outcome ascertained. Outcomes include: remaining in care, death, transfer to another clinic or loss to follow up (if tracing was unsuccessful). The database has monthly quality checks and is validated frequently.

Contribution of cohort data to the thesis:

These cohorts are well-established and contain data from a large number of patients on ART over more than a decade. In 2012, the iDART data from the Masiphumelele site was compared to the cohort data (without iDART), to determine whether the pharmacy database could monitor retention in care more accurately and efficiently than the standard cohort methodology (Chapter 4). Data from iDART was also incorporated into the randomised controlled study data (see below) after completion in July 2014 (Chapter 3). Viral loads and tablet return data for the randomised study were also retrieved from the cohort databases throughout 2012-2014 (Chapters 3 and 6).

Ethics Approvals:

The Desmond Tutu HIV Centre has had approval from the University of Cape Town Research Ethics Committee to collect routine clinical data on all individuals included in the HCTC and Masiphumelele databases since 2002 and 2004 respectively. This is renewed annually. The approval for 2015 is attached in Appendix 1.

Randomised controlled trial

The answers to many of the questions posed in the objectives could not be gleaned directly from the observational cohorts described above, and so I designed a 48-week randomised controlled trial (RCT).

The **TAP study**: A randomised controlled Trial to explore Adherence-failure relationships in a South African antiretroviral delivery site using an electronic adherence device and sparse Pharmacokinetic sampling, ran from July 2012 to July 2014 at the HCTC site. Protocol development was completed in early 2012, and staff (study coordinator, quality manager and 3 research assistants) were recruited in March 2012. The TAP study protocol is presented in Appendix 2. Participant recruitment began in July 2012 and was completed in March 2013. The final end of study visit occurred on the 4th July 2014.

This study explored the acceptability and impact of a locally produced, novel, wireless, electronic device, the Wisepill® [Figure 1.7], on adherence behaviour in

ART-naïve individuals commencing first-line ART at the HCTC. We hypothesised that the use of real-time electronic monitoring would reduce the overestimation of adherence seen with current methods. With the addition of a reminder sent by text message sent when dosing was late in the randomised arm, we hypothesised that the use of the Wisepill® would improve adherence, reduce treatment interruptions and subsequently reduce first-line ART failure rate. In 2010, up to 92% of South Africans carried cell phones, so the use of reminder text messages was considered feasible in our population. (85)

Adherence was also quantified at each study visit (weeks 16, 32 and 48 into treatment) using multiple methodologies including clinic based tablet return data, 3-day recall self-report and from the pharmacy refill data as imported to the cohort database from iDART.

Timed pharmacokinetic samples and samples for cytochrome 2B6 enzyme pharmacogenetic analyses were collected from all individuals who give consent.

Figure 1.7. Wisepill® electronic adherence monitoring device.



The study was funded by the European and Developing Countries Clinical Trials Partnership (EDCTP) through the mechanism of a Senior Fellowship, awarded in December 2011.

Contribution of the RCT data to the thesis:

The randomised data from this study was used to examine whether text messages sent soon after a missed ART dose could improve adherence and reduce treatment interruptions (Chapter 3). The six adherence measures collected from the individuals in the RCT were compared to determine which best predicted virological failure and the development of HIV-1 resistance (Chapter 6). EFV concentration and cytochrome 2B6 metaboliser status was used together with electronic adherence data to examine whether the utility of drug concentrations in predicting virological outcomes improves with knowledge of genotype and adherence status (Chapter 5). EFV concentrations were completed at the Division of Clinical Pharmacology laboratory, our collaborating partner for this project.

Ethics Approvals:

The TAP study received approval from the University of Cape Town Research Ethics Committee in May 2013 and had annual re-approval until July 2015, when the study was closed, on submission of the primary publication. Approvals are presented in Appendix 1.

Conflict of interest:

Although Wisepill® is a commercial business, the author declares no financial conflict of interest.

1.6. Overview and structure of the thesis.

The thesis includes an introduction (above) which places the importance of monitoring and improving antiretroviral adherence in context and describes the objectives of the thesis, which were conceptualised in 2012.

This is followed by a literature review, chapter 2, broken into two sections:

1. A systematic review of all studies with comparator arms and adherence as an outcome published from a resource –limited setting as completed by this author in early 2012. This was a sub-section of a larger review commissioned by the International Association of Physicians in AIDS Care (IAPAC): Guidelines for Improving Entry Into and Retention in Care and Antiretroviral Adherence for Persons with HIV - Evidence-Based Recommendations, published in mid-2012.(5) This review helped to guide and clarify objectives and intervention methodology for this thesis.
2. A systematic review of all studies in resource-poor setting using electronic methods, such as text messaging or automated voice messages to improve adherence. This review was conducted initially to inform the design of the intervention for this thesis in 2012 and has been updated regularly (last review July 2015).

Table 1-1: Link between thesis objectives, data sources and results chapters.

	Objective	Data source	Chapter
1	To explore the impact of real time electronic adherence monitoring device (Wisepill®) reminders on adherence, retention and virological outcome.	RCT Cohort data (Gugulethu)	3
2	To examine whether Intelligent Dispensing of Antiretroviral Therapy (iDART) can successfully monitor adherence and retention in care.	RCT Cohort data (Masiphumelele)	4, 6
3	To determine whether 2B6 pharmacogenetic data and efavirenz pharmacokinetics can predict treatment outcome.	RCT	5
4	To compare multiple different methods of quantifying adherence.	RCT	6

Four publications, either published or submitted for publication, are presented as results chapters (Table 1.2):

- Chapter 3, the published results of the RCT to determine whether text messaging when dosing is late can improve adherence and reduce treatment interruptions, addresses Objective 1.
- Chapter 4 presents a published brief report using cohort data which describes how the iDART system can be used to determine retention in care more easily than the current cohort monitoring system and, together with pharmacy refill data predicting virological and resistance outcomes from Chapter 6, fulfils Objective 2.
- The submitted manuscript presented as Chapter 5 uses data from the RCT to show that EFV levels, together with metaboliser genotype status data can predict virological outcomes, and determines an EFV predictive cut-off concentration. These data addresses Objective 3.
- Chapter 6 is a published paper comparing the predictive value of each of the adherence measures used to monitor the cohort during the RCT and completes Objective 4.

A final discussion to synthesise key messages from the thesis is presented in Chapter seven. Recommendation for future research and policy changes are made here. The conclusion summarises the novel contribution of the thesis.

2. Literature review.

2.1. Overview.

This literature review is in two parts. The objective of the first part is to discuss the published literature on methods to improve adherence to antiretroviral therapy in resource-poor settings. In 2012, when this review was completed, there was a relative paucity of well-structured randomised studies or studies with a comparator arm examining this topic. (27, 28) An update, based on recent reviews, have been included at the end of section 2.2 to bring this data up to date.

This first review allowed the author to consider which adherence interventions had been shown to be successful and to conceptualise the use of the Wisepill® electronic adherence monitoring device in the development of the randomised controlled study described above, as well as to elucidate objectives for this thesis.

The objective of the second part of the literature review was to examine in more detail the literature related to using automated electronic systems to monitor and improve adherence in a resource-poor setting. This review has been updated annually since 2012, with the last review of the literature completed in July 2015.

2.2. Part one - In a resource poor setting, which adherence interventions have proven to be successful?

Background

This review was undertaken in 2012 as part of a larger review of studies examining methods to improve adherence world-wide. Due to the few studies conducted in resource poor settings, the review did not differentiate between resource-rich and -poor settings. Studies were instead grouped by type of intervention. The data from resource-poor settings alone is presented for the first time here.(5)

Note: this systematic review described below was completed by the IAPAC review team. Once manuscripts were extracted, all those related to resource-poor setting were sent to this author for review and recommendation.

Search methodology

A systematic search for studies examining interventions to improve antiretroviral adherence and monitoring was performed. To be included, the study had to evaluate an intervention to improve adherence through either a randomised controlled design or through the use of a comparator arm. Either an adherence measure or a biological measure related to HIV, namely CD4 cell count or HIV-1 viral load, had to be used as the primary outcome measure. Observational data without comparator arms were not included. In addition, for studies to be forwarded to this author, the term “resource poor” or resource limited” was included in the key words. Countries that were considered “resource-poor” were those defined by the World Bank as having low or middle income economies, also known as “developing” economies.(86)

The following journal databases were searched: MEDLINE, EMBASE, CINAHL, as well as the Centers for Disease Control (CDC) and Prevention Research Synthesis database. Cochrane, Clinical Trials.gov and the Pan-African Clinical Trials Registry clinical trials databases were also searched. All searches included data from the commencement of each database up to the end of 2011. Conference abstracts from the Conference of Retroviral and Opportunistic infections, IAPAC adherence conferences, International AIDS Society conferences on HIV pathogenesis, Treatment and Prevention, were also searched from 2009 to 2011. For abstracts that have been published subsequently, the final manuscript was reviewed. Two reviewers employed by the CDC and funded by IAPAC extracted and coded the data for each study.

This search was updated in July 2015, with a search for recent reviews covering interventions to improve adherence to antiretroviral therapy in resource-poor setting. The search was completed using on-line electronic databases (PubMed and GoogleScholar) including the terms “HIV/human immunodeficiency virus – MeSH term” AND “Antiretroviral therapy/ART/HAART – MeSH term” AND “Adherence/adherent/compliant/non-compliance/non-adherence/treatment failure/treatment success/ viral suppression (non-compliance/compliance) – MeSH term”. We limited the search to review articles published in English after 2011.

Results of the 2012 review

Of 325 studies which met the above criteria in late 2011, only 24 (7.4%) were from resource-poor settings. This in itself was unexpectedly few, considering how, in many low- and middle-income countries, particularly in sub-Saharan Africa, the management of HIV, including delivery of ART is a key public health issue.

Considering further, that ART options are limited in such settings, due to the cost of drug and the large numbers of people requiring treatment, this lack of well-structured data on improvement of adherence could be having critical impact on ART programme outcomes.

The interventions in these 24 studies could be broadly categorised into six groups as per Table 2.1: directly observed therapy, education or counseling programmes, peer treatment supporters, food supplementation packages, programme structure (which included task-shifting) and electronic reminders.

Some studies included more than one intervention, for example, the study by Muñoz, et al used three combined interventions, published as two separate manuscripts. Within each group, while there was some consistency in methods of measuring outcomes, the interventions differed quite widely. This was particularly notable for the peer support and education/counseling interventions. The major findings for each group will be discussed below.

Table 2.1: adherence studies with comparator arms. Abbreviations are listed below the table.

Category 1	Category 2	Authors	Year	Country	Study Design	n	Intervention	Outcome
Directly observed therapy		Idoko, et al. (87)	2007	Nigeria	Non-randomised cohort study	175	DOT vs. SoC	CD4, VL
Directly observed therapy		Muñoz, et al. (88)	2010	Peru	Cohort, matched comparison	120	DOT vs. SoC	SR, CD4, VL
Directly observed therapy	Peer support	Nachega, et al. (89)	2010	South Africa	RCT	274	DOT vs. SoC	TR, CD4, VL
Directly observed therapy		Pearson, et al. (90)	2007	Mozambique	RCT	350	DOT vs. SoC	SR, CD4
Directly observed therapy		Sarna, et al. (91)	2008	Kenya	RCT	234	DOT vs. SoC	SR, TR, VL
Education / counseling		Mansoor, et al. (92)	2006	South Africa	RCT	120	Complex or simple patient information leaflet vs. SoC	SR, TR
Education / counseling		Oligbu, et al. (93)	2009	Nigeria	RCT	420	10 education modules vs. SoC	Retention, mortality
Education / counseling		Sampaio-Sa, et al. (94)	2008	Brazil	RCT	107	Group educational sessions vs. SoC	SR, PR, CD4, VL

Category 1	Category 2	Authors	Year	Country	Study Design	n	Intervention	Outcome
Education / counseling		van Loggenerberg, et al. (95)	2010	South Africa	RCT	297	Motivational interviewing vs. SoC	VL
Peer support		Chang, et al. (96)	2010	Uganda	RCT (clinics)	1336	Peer support (clinic and home-based) vs. SoC	TR, CD4, VL
Peer support		Muñoz, et al. (97)	2011	Peru	Cohort, matched comparison	120	Community-based care +/- microfinance vs. SoC	SR, CD4, VL
Peer support	Directly observed therapy	Mugusi, et al. (98)	2009	Tanzania	RCT	621	Dosing diary or peer support or DOT vs. SoC	SR, CD4, retention
Peer support	Directly observed therapy	Taiwo, et al. (99)	2009	Nigeria	RCT	499	Patient-selected treatment partner vs. SoC	PR, CD4, VL
Programme structure		Batavia, et al. (100)	2010	India	Cross-sectional study (4 arms)	635	Cost recovery programme vs. SoC	SR
Programme structure	Peer support	Kipp, et al. (101)	2010	Uganda	Non-randomised cohort study	385	Community based vs. hospital care	TR, CD4, VL
Programme structure		Matovu, et al. (102)	2011	Uganda	RCT	92	Nurse-peer vs. doctor-counsellor care	TR, CD4, VL
Programme structure		Sanne et al. (81)	2010	South Africa	RCT	806	Nurse vs. doctor care	VL, retention
Programme structure		Zachariah, et al. (103)	2007	Malawi	Within district cohort comparison	1634	Community support vs. none	PR, retention

Category 1	Category 2	Authors	Year	Country	Study Design	n	Intervention	Outcome
Food supplementation		Cantrell, et al. (104)	2007	Zambia	Cohort (stepped intervention by clinic)	636	Monthly food rations vs. SoC	PR, retention
Food supplementation		Serrano, et al. (105)	2010	Niger	Cohort, with comparator arm	180	Monthly food rations vs. SoC	TR, CD4
Electronic reminders	Education / counseling	Chung, et al. (106)	2011	Kenya	RCT	400	Education or alarm device or both vs. SoC	TR, VL
Electronic reminders		Lester, et al. (50)	2010	Kenya	RCT	538	Weekly SMS vs. SoC	SR, VL
Electronic reminders		Pop-Eleches, et al. (107)	2011	Kenya	RCT	431	SMS reminders vs. SoC	MEMS, TI
Electronic reminders		Sabin, et al. (62)	2009	China	RCT	68	Counseling if adherence drops vs SoC	MEMS, CD4
Electronic reminders		Uzma, et al. (108)	2011	Pakistan	RCT	76	Weekly phone call reminders vs. SoC	SR, CD4, VL

CD4: CD4 cell count; DOT: Directly observed therapy; MEMS: Medical Electronic Monitoring System; PR: pharmacy refill; RCT: Randomised controlled trial; SMS: Short messages or text messages; SoC: Standard of Care; SR: self-report, TI: Treatment interruption; TR: tablet return; VL: viral load.

Directly observed therapy (DOT):

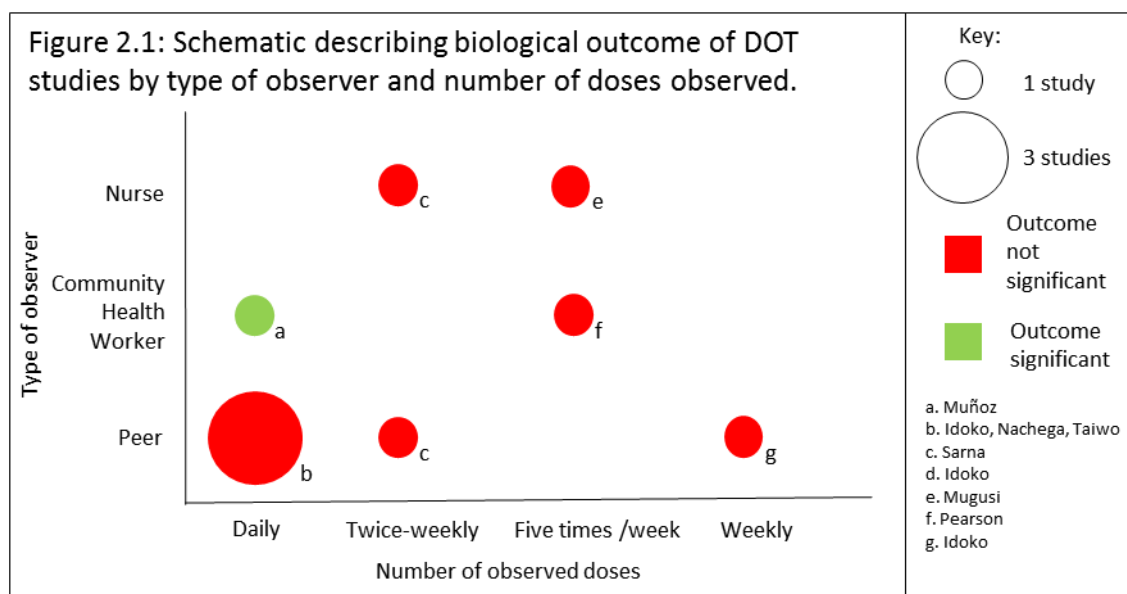
DOT refers to the observation of treatment doses by someone other than the patient. Five randomised studies and two cohort studies exploring the use of directly observed therapy in the context of ART in resource-poor settings had been published by 2012. (87-91, 98, 99) All, except one from Peru, were conducted in sub-Saharan Africa, and all included an ART-naïve adult population.

Not all DOT is equal, and in these studies it differed by cadre of observer, proportion of doses observed and duration of the observations. Idoko et al compared self-administered therapy to three versions of DOT: daily, twice weekly or weekly in a non-randomised cohort study over 48 weeks. The participants were observed by a treatment partner they had selected and who had received some training on adherence at the study clinic. (87) Muñoz et al, employed a DOT community team to observe every dose over a 12-month period. Those receiving DOT were matched by age and CD4 cell count to others in another study of community support, not using DOT. (88, 97).

The remaining five studies were RCT. Pearson et al randomised ART naïve adults to receive DOT on every daytime week day dose for six weeks, observed at home by lay staff employed by the clinic, compared to standard of care. Night-time doses and weekend doses were self-administered. (90) Nachega et al compared partial DOT (at least one daily dose) delivered by a patient-selected treatment partner, who received a short training session at the clinic, to others self-administering therapy over 24 months. (89) Taiwo et al also used patient-chosen treatment partners, who lived near to the participant, to observe dosing at home at least once a day for 48 weeks. They were compared to others receiving care at the same clinic without DOT. (99) Sarna et al used nurse-observed DOT twice a week at the clinic, with tracing for those who did not attend, compared to self-administered therapy. (91) Mugusi et al's study comprised three interventions: either morning dose DOT at the clinic for a month or peer support or a dosing diary, compared to standard of care. (98)

All of these studies used biological markers as a measure of outcome (CD4 cell count or viral load). One of the cohort studies did not use an adherence measure (87), and the others presented adherence data quantitated by either self-report (88, 90, 98), tablet return (89) or both (91). Taiwo used pharmacy refill data. (99)

All five of the RCTs and one of the cohort studies showed no benefit of DOT on increasing CD4 cell count or improving viral suppression over the full study duration [Figure 2.1]. (89-91, 98) DOT also did not have an impact on retention in most cases; though one RCT (90) showed some improvement in people remaining in care. Sarna and Taiwo et al both showed some improvement in adherence by self-report and tablet return, or pharmacy refill respectively. (91, 99) In Nachega's study, the intervention arm had reduced mortality compared to standard of care, possibly due to early benefits in increasing CD4 cell count, but this did not impact on virological response or CD4 improvement at 12 or 24 months. (89) The one cohort study that did show an improvement in adherence and viral suppression rates with DOT (Muñoz et al) had a number of limitations: the control group was less impoverished and the intervention enrolled more ill people. It was also difficult to tease out the impact of DOT compared with that of the community group intervention, which included microfinance support and food packages. (88)



Despite showing a few benefits, the overall impression of DOT is that it does not improve virological outcomes, thus does not achieve improvement in the main goal of ART. As three studies combined DOT with an aspect of peer support, it is also difficult to assign benefit to the observing of doses alone. (88, 89, 99) This is reflected in the recommendation not to use DOT in the IAPC review: “directly administered ART is not recommended for routine clinical care settings”. (5) DOT would be a complex and potentially expensive intervention to utilise on a large scale in resource-poor settings.

Education/Counseling:

Five randomised controlled studies included interventions linked to pre-treatment antiretroviral education or counselling. Again, all included ART-naïve adults as their study population. Two of these studies were South African, and the others were from Nigeria, Kenya and Brazil, see Table 2.2. (92-95, 106)

Three studies focused their education intervention on improving treatment literacy. Pre-treatment education was one component of the RCT intervention published by Chung et al. in Kenya.(106) The use of an alarm device was the other intervention, as described in the Electronic Reminder section above. The educational component included three group sessions of 30-45 minutes delivered by counselors; two delivered prior to ART commencement and one a month after starting. Content was practical, and included information on HIV, AIDS and ART, and explored personal barriers to adherence in the first month on therapy. Standard of care was a 15-minute explanation on ART dosing and potential side effects by the pharmacist as ART was dispensed. (106) The Brazilian RCT from Sampaio-Sa held small group education sessions (four sessions of 2-3 hours each) with similar content over two months around time of ART commencement, but they were staffed by a psychologist or social worker, rather than by a lay counselor. The control group were shown four short educational videos over a matching two-month period. (94) Oligbu, in an as yet unpublished RCT from Nigeria, compared 10 structured teaching modules, again covering information on HIV and ART and addressing possible adherence related issues, to casual teaching by nurses in the ward. All participants were hospitalised. (93)

The remaining two studies were more diverse: van Loggerenberg added an individualised intensive motivational interviewing intervention to the standard three treatment literacy sessions used in South Africa.(10) The sessions were client-centred and tailored to that participant. (95) The last RCT, published in 2006, randomised participant to receive either a complex or a simple patient-information leaflet to improve adherence to cotrimoxazole vs. no leaflet, after a short interview explaining the use of cotrimoxazole. (92)

Table 2.2: Outcomes of education-based studies. SoC as per South African ART guidelines.

Author	Intervention			Control			Outcome
	Type	Duration	Staff	Type	Duration	Staff	
Chung (106)	Treatment literacy, group	30-45 minutes x 3	Counsellor	Dispensing process	15minute x 1	Pharmacist	Improve TR, VL
Oligbu (93)	Treatment literacy, group	?duration x 10	Not specified	Casual	Not specified	Nurse	Improve (↓ mortality)
Sampaio-Sa (94)	Treatment literacy, group	2-3 hours x 4	Psychologist or social worker	Educational video	8-10 minutes x 4	None	NS change (TR, PR or VL)
Van Loggerenberg (95)	Treatment literacy, group PLUS individual motivational interviewing session	30-45 minutes x 3 PLUS 1	Counsellor	Treatment literacy, group	30-45 minutes x 3	Counselor	NS change (VL)
Mansoor (92)	Simple PIL, short information leaflet	15 minutes	Nurses	No leaflet, short information session	15 minutes	Nurses	Improved (TR, SR)
Mansoor (92)	Complex PIL, short information session	15 minutes	Nurses	No leaflet, short information session	15 minutes	Nurses	NS change (TR, SR)

Standard of care (SoC)

More than SoC

Less than SoC

Adherence was measured in three of the studies Chung, Mansoor and Sampaio-Sa, by either tablet return alone (106), tablet return and self-report (92) or tablet return and pharmacy refill data (94) respectively. Sampaio-Sa and Chung included both an adherence and a biological measure (VL) and van Loggerenberg only reported viral load outcomes. (94, 95, 106) Oligbu presented hospital stay and mortality data only.

Of the three studies focused on improving treatment literacy, two reported improved outcomes. Chung et al showed that the three education sessions improved adherence by

tablet returns by 6% at 18 months, as well as a reduced the chance of virological failure [Table 2,3].(106) Although not presenting an adherence measure, Oligbu found the 10 education sessions reduced hospital stay, readmission and mortality. (93) In contrast, Sampaio-Sa found no difference in adherence, CD4 or viral load outcomes between their four adherence group sessions and the short educational videos (94) Mansoor's study showed that simple patient information leaflets improved self-reported and tablet return adherence in the short term, but complex leaflets did not. (92) The study from van Loggerenberg, using individual motivational interviewing did not have an impact of viral load outcomes at 9 months.(95)

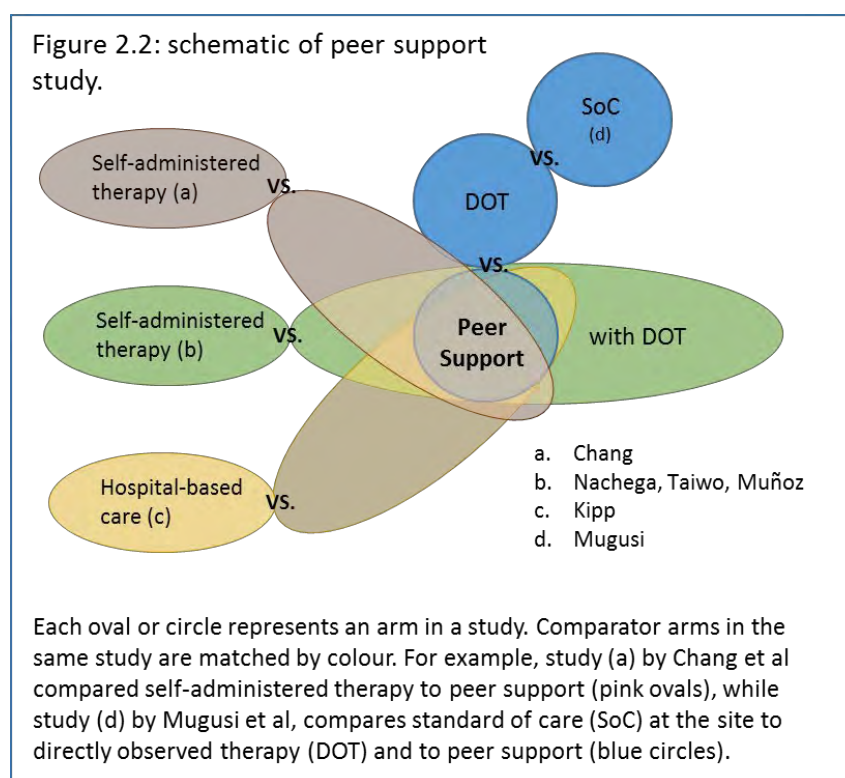
Although the interventions in these studies are diverse, the benefit of some pre-treatment education comes through. Chung and Oligbu compared structured education to minimal input and showed improvements in adherence, virological or mortality outcomes. (93, 106) Sampaio-Sa compared two difference methods of education, and saw no difference between the two. (94) Efforts to improve adherence beyond that gained from treatment literacy, by adding motivational interviewing did not prove successful [Table 2.3]. (95)

There are multiple recommendations related to education in the IAPAC review, and although the composite message is that education is beneficial, the evidence to support this recommendation is still not of the best quality. (5) Pre-treatment education is standard of care in South Africa. (10) In most resource-poor areas, the epidemic remains in the heterosexual adult population, not a marginalised population. The majority achieve viral suppression at a year. It seems likely that preparing people for ART is enough adherence input for this majority. More specialist adherence interventions, such as motivational interviewing, may prove to be of more benefit when focused on those noted to struggle with adherence later on.

Peer support:

For the sake of this review, a peer supporter is defined as an unpaid volunteer chosen by either the clinic, community or the study participant. Four RCTs and 2 cohort studies, all in ART-naïve adults, examined the impact of peer support on adherence. (89, 96-99, 101) All, except one from Peru, were from sub-Saharan Africa.

Three studies included some combined form of DOT and peer support as a single intervention [Figure 2.2]. (89, 97, 99). In Nachega's RCT, peer treatment supporters who were aware of the participant's HIV diagnosis were selected by the participant and attended initial clinic-based adherence and DOT training, which was reinforced every 3 months. In the self-administered arm, participants also selected someone for peer support, but with training on adherence only at ART commencement.(89) Participants in Taiwo's RCT also selected their own peer supporter, who received the same single training session that all study participants received as standard of care. The peer supporter was asked to observe dosing once a day and remind the participant when to pick up medication. (99) In Muñoz's complex cohort study, peer supporters were part of a team providing DOT, but the intervention also included microfinance loans and food baskets.(97)



The remaining three

RCTs used peer support alone [Figure 2.2]. Kipp et al offered community-based care to HIV-

positive individuals in a local sub-district and compared outcomes to those who attended the local hospital in a non-randomised cohort study. The community selected volunteer peer supporters to attend a two-day training on HIV ART, adherence and adverse effects. The peer supporters then visited each participant on ART in the sub-district weekly to count tablet returns and provide on-treatment support. In addition, each participant selected a family member for daily support. Peers could collect ART at the hospital for a participant if required. (101) Chang trained HIV-positive individuals to support others living with HIV, by providing ART counseling, and collecting self-report and tablet return adherence data at the participant's home every second week. Clinics in the health district were either randomised to utilise this peer support system or not.(96) One intervention arm of Mugusi's RCT included the use of patient-selected peer supporters who attended adherence counselling with the patient and then supported them at home. The other interventions were DOT (as described above), vs. standard of care. (98)

All studies used a biological measure as an outcome, either CD4 cell count or viral load. They also all used an adherence measure: either self-report (97, 98), or tablet return (89, 96, 101) or pharmacy refill. (99)

The 4 RCTs showed no improvement in CD4 count or HIV-1 RNA suppression at 1 year with the use of peer support. (89, 96, 98, 99) Taiwo's study showed an improved in adherence in those receiving adherence support which extended to 48 weeks.(99) However, in other the three studies peer support showed no improvement in adherence at 1 year compared to standard of care. (89, 96, 98) Kipp et al showed no difference in virological outcomes using peer supported community care compared to hospital-based care, perhaps more importantly showcasing a successful community model for treatment delivery, than the impact of peer support.(101) The only study which showed improvement in viral load and CD4 cell count was the complex cohort study by Muñoz, with multiple interventions that were difficult to disentangle.

While peer support is another attractive option for resource-poor settings, through the use of volunteers who can be incorporated into standard treatment literacy sessions rather than paid health care workers, there is little hard evidence to date that peer support results in improved outcomes on ART over time. The IAPAC review states: "peer support may be

considered”, but notes that the combination of the use of peer support together with other adherence interventions has resulted in limited evidence for benefit. (5)

Programme structure:

The five studies examining the improvements in adherence through altering the system of delivery of ART fall into two categories: task-shifting and cost recovery programmes. While neither would be considered a classic adherence interventions, these studies included adherence benefit as an outcome and so are included here. The one study on cost recovery originated in India (100), and the four describing the use of alternate cadres of health staff originated in sub-Saharan Africa. (81, 101-103) Support in the community by any staff employed by the care-system was considered task-shifting, as compared to volunteers chosen by the patient, defined as peer-support.

Batavia et al explored a system of cost-recovery at a large Indian hospital-based ART service. All patients attending the ART service were assigned to contribute 0, 50, 75 or 100% of medication costs according to their declared socio-economic status. (100) Two task-shifting RCTs compared nursing care with physician-based care for patients initiating ART. The first compared a nurse-peer model to the traditional doctor-counselor model over 12 months in an Ugandan hospital maternity unit.(102) The second study, from Sanne et al, randomised participants commencing ART to receive care from a nurse or a medical officer over 96 weeks in resource-poor communities in South Africa.(81)

The remaining two studies were cohort studies with various comparator arms. Kipp et al. describe rural community-based delivery of ART by community elected peer supporters who visited participants weekly and who could also collect ART for them. The district used was selected as it was some distance from the hospital and had traditionally limited ART access. Outcomes from the community were compared to those of participants receiving care at the hospital site.(101) Zachariah et al describes outcomes with a system of community support in some health districts of Malawi, compared to other districts without this support. Community activities were implemented by community nurses and volunteers who visited patients at home, and included identification of ill patients for referral, adherence support, HIV and ART education and income generations activities. (103)

Batavia et al. unfortunately used self-reported adherence alone to assess the impact of the cost recovery programme.(100) Sanne and Matovu presented results using CD4 and viral load outcomes. In addition Matovu used tablet returns to assess impact on adherence,

whereas Sanne did not note adherence outcome. (81, 102) Kipp et al also compared virological outcomes, but only collected tablet return adherence data for the community cohort.(101) Zachariah used pharmacy refill data to determine retention in care. (103)

Figure 2.3: Outcomes of task-shifting studies.

	Traditional care		Alternative care	Outcome
Matovu	Doctor-counsellor care (maternity unit)	vs.	Nurse-peer care (maternity unit)	Non-inferior (VL)
Sanne	Doctor-based care (clinic)	vs.	Nurse-based care (clinic)	Non-inferior (VL)
Zachariah	Clinic-based care (clinic)	+/-	Community –based care (nurses+peers)	20% better adherence (PR)
Kipp	Hospital clinic care	vs.	Community –based care (Peers)	Non-inferior (VL)

Batavia noted an improvement in adherence by self-report in those whose medication was completely funded: a 13% increase in those reporting adherence >95%. (100) Both Sanne and Matovu noted no significant difference (non-inferiority) in the proportion of those with viral load suppression by type of care delivery, and, for Matovu, no difference in adherence by tablet return by arm [Figure 2.3].(81, 102) Kipp showed excellent adherence in the community cohort, and similar viral load outcomes between the hospital and community cohorts.(101) Zachariah showed a 20% improvement in adherence in those with community support, together with a reduction in mortality and losses to care. (103)

It is important in a resource-poor setting that down referral of care was at least non-inferior, if not an improvement on standard medical-based care in all these studies. The IAPAC review incorporates this as a recommendation: “using nurse or community counselor based care has adherence and biological outcomes similar to those of doctor or clinic-based counselor care and is recommended in under-resourced settings”.(5) Innovative models of care are becoming more important as the number of individuals receiving ART in resource limited setting increase. New systems are required not only to relieve burden on medical

officers who are in short supply, but also to decongest clinics and provide alternative models of care for those who initiate ART with higher CD4 cells counts while clinically well.

Food supplementation:

Two studies from sub-Saharan African countries, Niger and Zambia, explored the use of monthly food supplementation packages on adherence to ART. Again, while the intervention here improves social welfare more directly than health, the outcome of these studies was adherence to ART and so these studies were included in the review. In both studies, adults who were ART-naïve and attending local government clinics were included. (104, 105)

These adult populations did differ: Serrano et al, from Niger, presented a cohort study with a comparator arm. All adults commencing ART as well as those pre-ART, were included in the cohort. Those with late stage HIV-disease (WHO clinical stage 3 or 4 and/or a CD4 cell count of <200 cells/mm³), or a body mass index of <18.5 kg/m² were eligible for six months of family nutritional support. This included cereals, legumes and vitamin A-enriched vegetable oils. (105) Cantrell's cohort study, in Zambia, included only adults with documented food insecurity. As the food supplementation programme roll-out across the health district was staggered, this allowed for comparison between people with documented food insecurity at clinics with the supplementation and those at clinics without. Participants again received six months of cereal, legumes and oil for six people. (104) Food rations were dispensed monthly in both studies.

Both studies showed substantial improvement in adherence by objective adherence measures: a 21% improvement in tablet returns over 6 months in those received supplementation in Niger (105) and a 22% improvement in medication possession as calculated from pharmacy refill data at 12 months in Zambia (104). The latter, Cantrell, did not note an improvement in CD4 cell count response, whereas Serrano noted a 1.7 times increase in CD4 cell count over the six months of the food supplementation programme.

The data from these two cohort studies were considered compelling enough to warrant a recommendation in the IAPAC review: "Interventions providing... resources to address food insecurity... are recommended". (5) Although such programmes are attractive in resource-poor settings, both studies were completed with donor food supplies from the World Food Programme. Without such donations, this is likely to be a costly intervention, and require some complex administration.

Electronic reminders:

In early 2012, there were five published randomised studies which used electronic monitoring or reminders to improve adherence, see Table 2.3. All studies were in HIV-1 positive adults new to ART, taking first-line non-nucleoside reverse transcriptase inhibitor-based treatment regimens. All three African studies were completed in Kenya, and two studies were from Pakistan and China. (50, 106-109)

Technology used in the interventions ranged from simple alarm devices (106) through medication event monitoring systems (MEMs caps) (109) to mobile phones (50, 107, 108). Uzma et al used mobile phones to allow research assistants to contact participants in the intervention arm by voice call once a week. Participants were reminded to avoid missing doses. (108) Both Lester et al and Pop-Eleches used short messages (SMS) or texts. Lester's bulk text message was sent once a week and included a simple enquiry: "How are you?" or "Mambo" in KiSwahili. Participants were asked to text one of two standardised replies, "I am fine" or "Sawa" vs. "I have a problem" or "Shida", within 48 hours. Those who did not respond or those that identified themselves as having a problem were called by a clinician to ascertain their status. (50) Pop-Eleches's team randomised one third of participants to standard of care and the rest to one of four different text message schedules: daily long or short message or weekly long or short messages. Short messages were simply reminders to dose and longer messages included some supportive text such as "be strong and courageous, we care about you." No reply was required. (107) Chung's study randomised participants to one of four arms with two possible adherence interventions: alarm device alone, education alone (3 sessions of 30-45 minutes delivered by a counselor), both or neither. The alarm device could fit in the participant's pocket, had to be carried at all times and beeped and flashed at the time doses were to be taken. (106) Sabin's study from China used MEMS data to determine participant adherence. Those who were non-adherent (<95%) were flagged for additional adherence counseling, including review of the MEMS printout and an exploration of reasons for missed dosing. (62)

In four studies, a biological measure was used as an outcome as well as an adherence methodology. A suppressed viral load is considered to constitute successful ART, but only three of the five studies included virological outcomes. (50, 106, 108) A fourth used

improvement in CD4 count. (109) The other study relied on adherence measures alone to determine success. (107) No study used self-reported adherence as the sole outcome. If no biological measures were used, either MEMS or tablet returns were used to quantitate adherence. (106, 107)

Table 2.3: Adherence and biological outcomes of electronic reminder intervention studies.

	No clinic feedback			With clinic feedback		
Author	Chung	Pop-Eleches	Pop-Eleches	Lester	Sabin	Uzma
Type of intervention	Alarm device	Daily text	Weekly text	Text message	MEMS and counseling	Voice call
Biological outcome	NS (VL)	-	-	Significant (VL)	Significant (CD4)	Significant (VL)
Adherence outcome	NS (TR)	NS (MEMS)	Improved (MEMS)	Improved (SR)	Improved (MEMS)	Improved (SR)

Two of the studies, by Lester and Sabin, using weekly cell phone text enquiry with replies or MEMS monitoring with adherence feedback respectively, showed that the use of these electronic devices linked to clinic contact improved adherence by 12% at 12 months into ART [Table 2.2]. (50, 62) Each of these studies also confirmed improvement in outcomes using a biological marker (decrease in HIV-1 RNA and increase in CD4 cell count respectively).

However, a third well-powered RCT in Kenya (Pop-Eleches et al) showed that weekly text message reminders *without* any further clinic contact also improved adherence: 13% more people maintained more than 90% MEMS adherence over 48 weeks and treatment interruptions of 48 hours or more were reduced. The long or short message content did not impact on outcome, and neither did the daily messages. Daily message were assumed to cause message fatigue in the participant and thus to be ignored. No biological outcomes

were presented. (107) A short RCT (Uzma) with only 8 weeks of follow-up showed benefit on self-reported adherence of a weekly phone call from clinic staff to participants on ART, with an increase in virological suppression.(108) One RCT (Chung) showed that an alarm alone (with no feedback) had no benefit on adherence as measured by pill count or on biological outcomes at 18 months into treatment. (106)

The success of the weekly text messages in the two Kenyan studies, lead to the recommendation by the IAPAC group that technology, with a link to care, be included as adherence support: “Reminder devices and the use of communication technologies with an interactive component are recommended”. (5) This was echoed by the World Health Organisation in their 2013 ART guidelines: “Mobile phone text messages could be considered as a reminder tool for promoting adherence to ART as part of a package of adherence interventions”. (110, 111)

Not all these studies will easily to expand to scale in a resource-poor setting. The three studies with improvements in CD4 cell count and viral load suppression all required direct interaction with another skilled human being: participants were called either as a routine or on their request, or received additional education at the clinic.(50, 108, 109) Only one of the two studies that did not require increased human resource input showed an improvement in adherence. Weekly text messages improved adherence measured by MEMS, but an alarm device had no impact on adherence as measured by tablet returns. The use of technology itself is a very attractive option in resource-poor setting due the possibilities of easily reaching many people in an acceptable manner, with little systematic cost or effort. However, further exploration of the use of text messaging, in more diverse settings should be undertaken before these recommendations become entrenched.

Review update and discussion

The search for new studies with adherence as an outcome and a comparator arm conducted in July 2015, found that most of the new articles and reviews relating to adherence were focused on electronic adherence interventions. These articles are covered in the second part of this review (page 67).

Three other recent reviews have focused on all adherence interventions in ART:

Barnighausen *et al.* conducted a review of adherence literature in a sub-Saharan Africa, also in late 2011; Chaiyachati *et al.* conducted a review of all interventions to improve adherence to antiretroviral therapy in 2014; and Mbuagbaw *et al.* reviewed interventions for enhancing adherence to ART in high quality studies in May 2015. (111-113).

Barnighausen *et al.* conducted a review of studies to evaluate adherence specifically in sub-Saharan Africa, at the same time as the IAPAC review was being conducted. Any ART study with adherence outcome and a control or comparator group was included. They identified 26 studies, and described similar intervention categories to those used above: structured teaching programmes, treatment supporters, directly observed therapy, mobile phone text messages, changes in programme structure, including task shifting, and food rations. All of these improved adherence in this setting. They also noted that 14 of the studies used more than one intervention simultaneously; and that discrepant findings for a single intervention were commonplace. Of note, they concluded DOT to be of benefit, despite this review including four of the five papers I reviewed above. This was based on a 2010 meta-analysis by Hart *et al.* which noted benefit of DOT when observational studies were included in the analysis, though not if only randomised studies were used. (112, 114)

Chaiyachati *et al.* conducted a rapid systematic review (a review of previous reviews) of adherence interventions in both resource-rich and –poor settings, to inform the 2013 WHO antiretroviral guidelines. They only included recent reviews and RCTs conducted in the two years prior to the search. Their review again categorised studies into similar groups: “education, cognitive-behavioural interventions, treatment supporters, directly observed therapy, and active adherence reminder devices (such as mobile phone text messages)”. Each group had been tested in 20 or more rigorously conducted studies. The review included the majority of the studies identified by this author as well. They noted that while

each intervention group tested above has been shown to improve adherence through a number of rigorous studies, each intervention has also been found not to have an impact in similarly rigorous settings e.g. DOTs is a good strategy for prison populations, but not in other settings. They note that adherence is a form of behaviour and as such will be altered by “culture and circumstance”.(111)

The final review, by Mbuagbaw, examined high quality studies with both a clinical (viral load or CD4 count) and an adherence outcome with follow-up of at least 80% of the cohort for a minimum of six months. Studies were not limited to resource-poor settings. Forty-nine studies were included in the results, of which only 10 had both adherence and clinical benefit. Factors which resulted in the success of these 10 were unclear. Successful study interventions included: dose simplification, text messages, use of a web-based life-skills programme, counselling and motivational interviewing. (113)

To conclude, there are relatively few studies from resource-poor settings that examine interventions that might improve ART adherence. All of the interventions above could be supported by further evidence. Many studies examine more than one intervention at the same time (e.g. peer-support and DOT), making it difficult to evaluate which intervention has an impact on adherence. In addition, all the interventional studies discussed were of relatively short duration (12 to 18 months) making it impossible to project sustainability. Cost is an important consideration for interventions aiming to improve ART adherence in resource-poor settings: therefore there is a need for cost-effectiveness analysis for any effective ART adherence interventions, which is also currently lacking.

Finally, in resource- poor settings, with few resources and large patient numbers, non-adherent patients requiring additional counseling and support often compete for staff and clinic resources that are also needed to initiate people on ART. A number of studies reviewed here, as well as more recent studies, are focused on decentralising and simplifying ART care and support through task-shifting, peer education groups and peer-or community-based care. (13, 101-103, 115) Further exploration of support using electronic reminders could aid in this decentralization. Such programmatic approaches to optimise the use of clinic staff might markedly reduce the burden on ART clinics without worsening adherence or biological outcomes, but these approaches will require more evaluation.

Contribution of this review to the development of the thesis

Of the adherence interventions described above, those with the most success appeared to be pre-treatment literacy or education, task-shifting, food supplements and electronic reminders. The evidence for the use of peer support was minimal, and randomised studies using DOT only showed minimal benefit.

By 2012, the South African ART programme had already task-shifted toward minimising the use of medical officers and increasing the use of nursing staff; using evidence from two large South African studies, CIPRA-1 and STRETCH.(81, 116) In addition, research at the HCTC site in shifting models of care from nurse-based at the clinic to counselor-based in off-site adherence clubs was already underway.(13) The South African ART guidelines also stipulated that three counselor-based group treatment literacy sessions should be offered to each ART-naïve participant.(10) The HCTC site has offered these structured group sessions since 2002, both in clinic hours and at weekends. (38) Food supplementation, although not ideal, is offered to those with concomitant tuberculosis and a low body mass index.

Two areas of interest stood out for this author. The first was that, in all the studies reviewed above, there was no standard methodology for monitoring adherence. The second was that the intervention which seemed most promising for scaling up ART in a resource- poor setting and the one with the most scope for new knowledge was the use of electronic reminders, via a mobile phone. An intervention which could improve adherence and possibly retention in care, and that could be disseminated widely without requiring extra human resources would be very attractive. One large study from Kenya showed an improvement in adherence with the simple addition of weekly text messages. (107)

In addition, Lloyd Marshall of Wisepill® had approached the Desmond Tutu HIV Foundation with his device. Early data showed use of this device to be acceptable and feasible.(60) The use of this device to monitor adherence, coupled with the capability of sending text reminders linked to ART missed dosing, and so avoiding message fatigue from routine messaging, seemed a unique opportunity to explore adherence measuring methodology and whether linking reminders directly to missed doses would impact on adherence and retention. This novel real-time approach to reminders had not been published before, and

solved two problems in one – finding a quality method of monitoring adherence and intervening rapidly with little human resource input required.

2.3. Part two- Impact of use of mobile phone technology on adherence to ART in resource-poor settings.

Background

As discussed in the introduction to this thesis (page 17), with the number of people living with HIV in resource-poor settings who need to be commenced on ART increasing, as newer country guidelines allow access to ART with higher CD4 cell counts, maintaining each individual in care, with high levels of adherence to first-line therapy becomes increasingly challenging.(10, 110) However, the mobile phone network has similarly expanded in many resource-poor areas over the past 10 years and most sub-Saharan African countries have extensive networks, at least in urban areas. In 2010 South Africa had more mobile phones than there were people [Figure 2.4]. (85)

Figure 2.4: Gapminder bubble chart showing South Africa to have 101 mobile phone subscribers per 100 people in 2010 (ringed blue bubble). Each country is represented by a bubble. The size of each bubble reflects the total population of each country, and the colour of the bubble indicates the continent as per the small map in the top right of the figure. The x-axis marks the income per capita and the y-axis the number of mobile phones per 100 people. (85)



Initial studies using mobile phone voice calls in support of ART adherence have been published from 2005, but with mixed results. (108, 117, 118) While Uzma at al, showed adherence and biological

benefit from a randomised voice call study in Pakistan, another randomised study from the United States showed that 16 scripted calls by nurses to participants over 96 weeks did not improve adherence or virological outcomes. (108, 118) A more recent study, from Huang et al in China, also showed no benefit from a call to a mobile phone every second week.(117) Voice calls also require the time of an at least semi-skilled staff member. Human resources are finite in the face of the growing number of people taking ART, and there is much focus on task-shifting away from medical and nursing staff, as well as down-referral to more peripheral clinics and even community sites. (13, 81, 116) Relying on support to individuals through voice calls is unlikely to be feasible.

The use of mobile phone technology to support adherence is more easily scalable and affordable. Adherence support which is not focused on a health facility is also attractive, as the numbers of those on treatment who have never been ill increases. Such technology may also be more attractive to the young, who are more at risk of loss to care over time. Of the five randomised studies examining the use of electronic reminders described in the above review [Table 2.2], two studies from Kenya showed benefit of using text messages in improving adherence and possibly virological outcome. (50, 107) The World Health Organisation 2013 ART guidelines subsequently embraced the use of technology. (110) Initial reviews of the use of mobile phone messaging were enthusiastic in suggesting the use of automated technology might improve adherence (119-121). However, more recent studies, reviewed below, suggest the benefit may not be as universal as initially thought.

This review will examine the evidence for the use of automated systems to send mobile phone reminders to improve adherence in ART in resource- poor settings; and examine cohort characteristics to determine whether particular subgroups may benefit more from such automated interventions than others.

Search methodology

The objectives of this review were to summarise the findings of any randomised controlled trial examining the impact of mobile phone messaging, compared to standard of care, on adherence to antiretroviral therapy with focus on those conducted in a resource poor setting. Secondary objectives were to see whether particular populations benefit more than others from text messaging, and whether messaging characteristics might be more or less beneficial than others e.g. message frequency, message content and the need for a response to the message.

Search strategy: the review was approached systematically; the author searched on-line electronic databases, using the terms “HIV/human immunodeficiency virus – MeSH term” AND “Antiretroviral therapy/ART/HAART – MeSH term” AND “Adherence/adherent/compliant/non-compliance/non-adherence/treatment failure/treatment success/ viral suppression (non-compliance/compliance) – MeSH term” AND “Mobile phone” OR “text messages”. We limited the search to articles published in English after 1995.

The same searches were conducted in each of the following databases: MEDLINE (via PubMed), Africa-Wide (NIPAD), SCOPUS (Web of Science), Cochrane Central Register of Controlled Trials and Literatura Latino-Americana e do Caribe em Ciências da Saúde (LILACS).

Types of studies: Only randomised controlled studies were included in the review. Primary outcome was either any measure of antiretroviral adherence or a biological measure, namely HIV-1 viral suppression or increase in CD4 cell count at the end of the study. Study populations included HIV-positive adults, adolescents or children taking treatment for HIV. Interventions using mobile phone messaging, or automated calls, were included.

Data collection: The results of each search were imported into a reference manager programme (EndNoteX7®). Duplicate references were removed. The author reviewed all titles and abstracts, using titles, abstracts and other describing information to identify those articles which met the inclusion criteria based on study design, population included, type of

intervention and outcome measure. The full text was obtained for each of these article identified and the references of these studies also searched for further relevant articles.

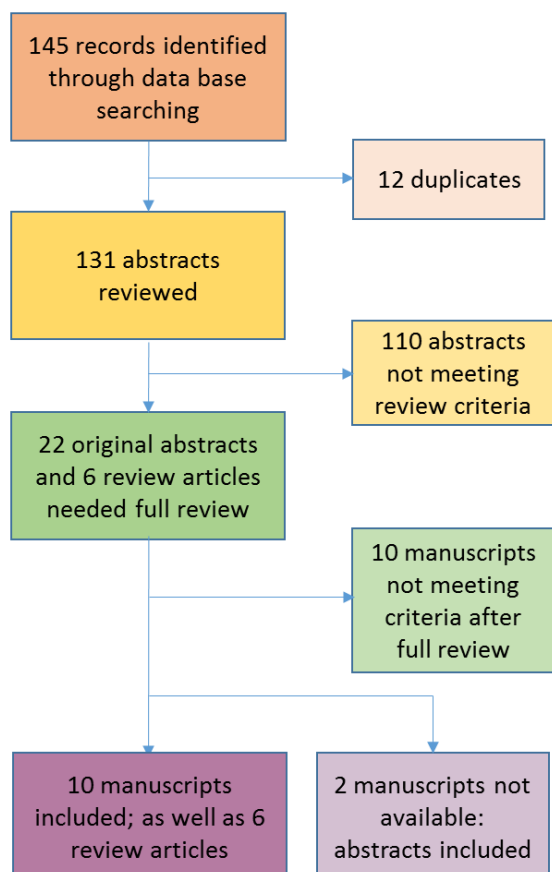
Data extraction: the author extracted data into a data table which include the following fields: study design, including details of randomisation (to assess for bias), location, clinic setting, duration and year of publication; participant number and age; intervention details including type and frequency of intervention, message content, whether messaging was manual or automated and requirement for response to the message; outcome measures, including method of measuring adherence, CD4 count, HIV-1 viral load and the outcome results. Outcomes were summarised as no difference, improvement in adherence alone and improvement in adherence and biological marker.

Data analysis: as there was little consistency between the outcome measures and intervention used amongst the studies, a narrative descriptive review is summarised below. Where necessary, intervention variables were compared with the outcome summary using proportions and percentages.

Results

The search was repeated three times between January 2014 and August 2015. Figure 2.5. is a flow diagram showing the number of studies identified, and those reaching the final review.

Figure 2.5. Study flow diagram



The field of mobile phone reminders is growing rapidly.(122) For example, in PUBMED there were 36 hits using the above search terms in March 2014 and 56 by August 2015. There were 12 duplicates in the combined 145 hits from searched databases. After review of these abstracts, 22 full text articles were selected for retrieval. That there have been six reviews of the topic since 2011, is a measure of the global interest in mobile phone reminder systems: three reviews focus solely on these interventions in ART (119-121) and another three reviews on broader ART adherence interventions, including sections on electronic reminders. (5, 111, 112)

Of the 22 original publications which met inclusion criteria on initial review of the abstract, 20 were reviewed in their entirety [Figure 2.5]. Two manuscripts could not be sourced (one

unpublished abstract and one unpublished thesis). Ten manuscripts were subsequently excluded for the following reasons: four had not yet published results (123-126), four used voice calls and not an automated system (108, 117, 118, 127) and the remaining two were not randomised studies (128, 129).

Reviewed studies: structure and population.

There were 12 studies which met all the inclusion criteria for the review i.e. randomised studies examining the use of electronic reminders to improve adherence in a population taking ART. Eight were conducted in a resource-poor setting. Full manuscripts were not sourced for two of them. (130, 131) Each study is described below, with the structure of the study, the included population and a summary of each intervention presented in Table 2.4; and the intervention details, outcome measures and results in Table 2.5.

Bigna et al published a study examining the impact of mobile phone-based reminders on adherence to care for 242 parent-child pairs attending hospital-based paediatric clinics in three different districts in Cameroon [Table 2.4]. This is the only study including children. Pairs were randomised 1:1:1:1 to one of four arms: 1. standard of care, 2. SoC and a text message 48 hours before their appointment, 3. SoC and a call 48 hours before their appointment or 4. a text reminder 72 hours before AND a call 48 hours before the appointment. Calls and texts were completed by a staff member and included identical information: the date and time of their appointment as well as the address of the hospital and the treating doctor's name. No messages were left on mobile phones. The median age of the children ranged from 1.8 to 5.0 years between the groups and that of the adults from 36.5 to 50.5 years. Outcome was measured as the efficacy of each intervention, calculated as the proportion in each arm who attended their appointment. Attendance on the day of appointment was low (51%) in the SoC arm, compared to 75-89% in the intervention arms.

Voice calls and / or text messaging improved visit attendance in parent-child pairs in this short study from Cameroon.

Using intention to treat analysis, the odds of attendance were improved in all three arms [Table 2.5], with no significant difference noted between the interventions. While the data

presented of good quality, the study was very short: completed within three months, as only one appointment per parent-child pair was included. No biological outcomes were collected. (132)

A Brazilian study, by da Costa et al, assessed the effect of a text message intervention in women on ART at a hospital-based ART clinic. The participants were adults, and both ART-naïve and non-naïve, had been on ART for at least three months and had a suppressed viral load. Women who owned mobile phones were randomised 1:1 to either SoC (which included treatment literacy) or SoC and only daily text message reminder timed 30 minutes pre-dose, five times a week (Monday, Wednesday, Friday, Saturday and Sunday) [Table 2.4]. Messages were sent using an automated web-based system, and the content of the

Text messages did not impact on adherence in women from Brazil in this short low quality study.

messages was the same “Take good care of your health” over 4 months. Adherence was measure using self-report, tablet returns and MEMS. The methods stated that CD4 and viral load data was collected, yet no results were presented. Recruitment was poor: only 29 women entered to the study. Data is only reported on 21 of these women [Table 2.5]. The study was underpowered, and despite excluding women who did not complete the study, showed was no improvement in adherence by any measure. (52)

Hardy et al examined the use of a personalised reminder system in the United States. Adult participants with self-reported poor adherence (<85%) at three or more months into ART were drawn from a tertiary hospital setting and were randomised 1:1 to either receive a beeper or a mobile phone, as well as \$30 cash incentive for each visit (\$90 in total). The beeper gave a single reminder beep at the time of dosing. Those who received mobile

This short study showed that text messages improved adherence in a small number of people from the United States.

phones were sent daily personalized text messages as reminders instead [Table 2.4]. Content was drawn from a participant interview and could include a joke, weather updates or current news items. The intervention ran for 6 weeks and adherence was measured using self-report, tablet return and MEMS. No biological outcomes were reported. Twenty-three participants, with a median age of 43 years, were randomised, and 19 completed the study. Data is only reported on these 19. MEMS adherence was significantly higher in the text message arm, but did not differ by other measures [Table 2.5].

Ikeda et al presented an abstract at the International AIDS conference in 2012, which has not yet been published. This group used text messaging to explore improvements in viral load outcome in Guatemala, where, like South Africa, there are more registered mobile phones than people. HIV-positive adults initiating ART at a clinic were randomised to receive

Text messaging improves viral suppression at 12 months in this study from Guatemala.

a reminder text message at the time of their evening dose, for three months and could also call an educator if needed [Table 2.4]. Outcome was time to first viral load suppression, and suppression at 12 months. No adherence was quantified. The 118 people in the intervention arm achieved viral suppression in a median time of seven months, compared to 10 months in the 108 people in the control arm. At 12 months, those in the intervention arm were at lower risk of viral failure than the control arm: RR 0.36, 95%CI 0.25-0.51). Some details of this study, such as power, randomisation process and messaging system used are not specified in the abstract, so it was not possible to fully assess study quality [Table 2.5].(130)

Table 2.4 Reviewed studies, structure, population and structure of interventions

Author name	Year	Country	n	Setting	Study design	Type of patient	Randomisation	Control	Intervention
Bigna (132) (MORE CARE)	2014	Cameroon	242	3 district hospitals: urban, semi-urban & rural.	RCT	Adult-child pairs (naïve or non-naïve)	Block randomization 1:1:1:1, well-described.	SoC: no pre-visit text message or call	<ul style="list-style-type: none"> • SMS (48hours before visit) or • Call (48hours before visit) or • SMS (72hours) and call (48hours) before visit
da Costa (52)	2012	Brazil	29	Tertiary hospital	RCT	Adult women (naïve or non-naïve), VL suppressed.	1:1, in blocks of 20, well-described	SoC: treatment literacy by multi-disciplinary team (blinded to arm).	SMS timed before dosing M/W/F/S/S.
Hardy(51)	2011	United States	23	Tertiary hospital	RCT	Adults noted non-adherent (SR<85%); ≥3 months on ART.	1:1, well-described.	Beeper at time of dosing	SMS: personalised texts daily at time of dosing. Given a mobile phone (to standardise, but allowed unlimited calling). SMS reply required
Ikeda (130)	2012	Guatemala	226	Outpatient HIV clinic	RCT	Adults, naïve	Not stated (abstract only)	SoC: instruction on medication dosing at monthly visits.	SMS reminder at time of evening dose for 3 months; 24-hour number for an educator.
Lester (50) (WelTel Kenya1)	2010	Kenya	538	3 outpatient HIV clinics: diverse settings	RCT	Adults, naïve	1:1 random number generating programme.	SoC: 3 counselling sessions as started ART (2 pre-ART, 1 at month 1). Support group encouraged.	SMS on Mondays with health enquiry. SMS reply required. Called if no response within 48 hours.
Maduka (53)	2013	Nigeria	104	Tertiary hospital	RCT	Adults noted non-adherent (<95%); ≥3 months on ART.	1:1, process clear.	SoC: pre-treatment education in a group; admonitions by doctors or pharmacists at visits.	SMS twice weekly. SMS reply preferred. Called if requested. AND monthly 1 on 1 adherence counselling
Mbuagbaw (133) (CAMPS)	2012	Cameroon	200	District hospital.	RCT	Adults, ≥1month on ART	1:1, process clear.	SoC	SMS weekly, phone number to call if needed.

Author name	Year	Country	n	Setting	Study design	Type of patient	Randomisation	Control	Intervention
Musser (131)	2001	US	22	Not specified.	RCT	Adults, non-naïve. VL suppressed.	Not specified	SoC	SMS: daily messages x 2 weeks. SMS reply required.
Orrell (134)	2015	South Africa	230	Outpatient HIV clinic	RCT	Adults, ART naïve	1:1, process clear.	SoC (3 pre-ART education sessions and a home visit)	SMS if dosing more than 30minutes late; Adherence reports in clinic folder for clinicians to review.
Pop-Eleches (107)	2011	Kenya	431	Outpatient HIV clinic	RCT	Adults , <3months on ART	1/3 to control, 2/3 allocated 1:1:1:1 to intervention.	SoC (n=139)	<ul style="list-style-type: none"> • SMS daily – long, or • SMS daily – short, or • SMS weekly – long, or • SMS weekly – short. Given a Nokia phone.
Sabin (62)	2015	China	120	Outpatient HIV clinic	RCT	Adults, naïve. stratified by adherence at 3 months.	Two strata - optimal (≥95%) or suboptimal adherence. Both randomised.	SoC	SMS if dosing more than 30minutes late; Adherence reports discussed with participant at visits.
Shet (135)	2014	India	631	2 public sector private sector outpatient HIV clinics	RCT	Adults, ART naïve	1:1, process clear.	SoC (three pre-ART counselling sessions)	Automated voice call: weekly, which required a response (4 call attempts). SMS sent out 4 days after weekly message. Given mobile phone.

ART = antiretroviral therapy n = number; RCT = randomised controlled trial; SoC = standard of care; SMS = text message; VL = viral load.

Table 2.5. Reviewed studies – intervention details, outcome measures and results.

Author	Intervention	Message content	Message timing	Auto-mated	Required response?	Adherence measure	Biological measure	Duration	Outcome	Criticism	Outcome summary
Bigna (132) (MORE CARE)	SMS or call	Date and time of visit, clinic name and name of doctor.	Before a clinic visit	No	No –used delivery notification.	Efficacy: adherence to clinic visit / presence at appt (%)	None	3 months	Efficacy cf. control: • SMS only OR 2.9 (CI 1.3-6.3); • Call only OR 5.5 (CI 2.3-13.1); • Both OR 7.5 (CI 2.9-19.0) NS difference between arms and no synergy.	Short: intervention used for only 1 appointment per pair.	Adherence better
da Costa (52)	SMS	"Take good care of your health"	Pre-dose, M/W/F /S/S	Yes	No	SR (30 days), TR and MEMS	None	4 months	Adherence (%>95%) by (C vs I): • SR 84% vs 100% (p=0.24) • TR 38% vs 50% (p=0.60) • MEMS 46% vs 75% (p=0.19) NS by any adherence measure	Short: Not ITT - randomised 29, presented 21.	NS
Hardy (51)	SMS or beeper	Varying, drawn from patient interviews (jokes, news, weather)	Daily, pre-dose	Yes	Yes	SR (7 day), TR and MEMs	None	1.5 months	Adherence (%) by (C vs. I): • SR 72% vs 92% (p=0.07) • TR 69% vs 83% (p=0.15) • MEMS 56% vs 90% (p<0.01).	Short. Not ITT – randomised 23, presented 19.	Adherence better
Ikeda (130)	SMS	Not specified	Daily, pre-dose	Not specified	No	None	VL	12 months	Increased VL suppression in intervention arm at 12 months: RR 0.36 (CI 0.25-0.51))	Not yet published	Biological better
Lester (50) (WelTel Kenya1)	SMS	"How are you?" Response: "well" or "problem".	Weekly (M morning)	No	Yes	SR (30 days)	VL	12 months	Adherence (%>95%) by (C vs I): • SR 49% vs 62%, RR 0.81(CI 0.69-0.94) and VL suppression: (C vs I) 48% vs 57%, RR 0.84 (CI 0.71-0.99)		Adherence and biological better
Maduka (53)	SMS and counselling	Pre-scripted, adherence information and dosing reminder.	Twice weekly (M/Th morning)	Yes	Yes (preferred)	SR (7 day)	CD4	4 months	Adherence (%>95%) by (C vs I): • SR 55% vs 77% (p=0.02). CD4 count increase (C vs I): 231 vs 382 (p<0.01).	Combination strategy used; effect may be from counselling.	Adherence and biological better

Author	Intervention	Message content	Message timing	Automated	Required response?	Adherence measure	Biological measure	Duration	Outcome	Criticism	Outcome summary
Mbuagbaw (133) (CAMPS)	SMS	11 varied motivational messages, with phone number.	Weekly (W morning)	No	No – used delivery notification.	SR (7 day), VAS (7 day) PR	None	6 months	Adherence (%>95%) by (C vs I): • SR RR1.01 (CI 0.87-1.16), • VAS RR1.06 (CI 0.89-1.29), • PR mean difference 0.1 (CI - 0.23-0.43).	No biological outcome.	NS
Musser (131)	SMS	Uniform reminder message	Daily	Not given	Yes.	SR (14day)	None	0.5 months	Adherence (%): • SR OR2.03 (0.48-8.48)	No biological outcome.	NS
Orrell (134)	SMS	5 short reminder messages, chosen by participants	30 minutes after missed dosing	Yes	No	Wisepill (electronic pill box)	VL	12 months	Adherence(%) by (C vs I): • Electronic cumulative 80% vs 82%, OR1.08 (CI 0.77-1.52) VL <40 copies/ml (C vs I): 69% vs 65%, OR 0.77 (CI 0.42-1.4)		NS
Pop-Eleches (107)	SMS	Short: reminder. Long: reminder & motivational message.	Daily or weekly, midday.	Yes	No	MEMs (3TC)	None	12.. months	Adherence (%>90%) by (C vs I): • MEMS 40% vs 53% (p=0.03) weekly. • MEMS 40% vs 47% (p=0.27) daily Content of message: NS.	No biological outcome	Adherence better
Sabin (62)	SMS	10 short, reminder messages chosen by participants.	30 minutes after missed dosing	Yes	No	Wisepill (electronic)	CD4 VL	6 months	Adherence (%) by (C vs I): • Electronic 89% vs 96% (p<0.01); similar for both strata. CD4 increase (C vs I): 28 vs 52 (p=0.3); VL <40 copies/ml (C vs I) 94% vs 98% (p=0.22)		Adherence better
Shet (136)	Automated voice call	Customised motivational message, dosing enquiry. Pictorial SMS 4 days later.	Weekly call, weekly SMS.	Yes	Yes	TR	VL	24 months	Adherence (%<95%) by (C Vs I): TR 22% vs 27%, IRR 1.24 (CI 0.93-1.65) VL >400 copies/ml (C vs I): 15.5% vs 15.6%, HR 0.98 (CI 0.67-1.45).	Unclear if LTFU (7-9%) and deaths (6-7%) were classified as complete or as failures.	NS

Adh = adherence; apt = appointment; C vs I = control vs intervention; CI = 95% confidence intervals; HR = hazard ratio; IRR = Incidence rate ratio; ITT = intention to treat;

LTFU = loss to follow-up; NS = not significant; OR = odds ratio; RR = relative risk; SoC = standard of care; VL = viral load.

The study from Lester et al published in 2010 was the initial study that showed benefit of weekly text messages with improvement in both adherence and virological outcomes in an ART-naïve cohort from Kenya. This study was reviewed above (page 60). Standard of care included treatment literacy sessions before starting ART and support groups were encouraged. Weekly enquiries after a participant's health were sent as a text message those in the intervention arm and a response was required. Those who requested input and non-responders were called by a nurse [Table 2.4]. Both adherence (SR) and biological outcomes (VL) were assessed. The median age of participants was 37 years. The text message intervention significantly improved both adherence and virological outcomes [Table 2.5]. The study data was of good quality, it was well-powered and the randomization process was clear. Both intention to treat and per-protocol analyses were presented. This study, together with the study from Pop-Eleches, forms the basis of many recommendation to use electronic reminders to improve ART outcomes. (50, 107)

This mixed intervention study from Nigeria showed that text messages and counselling improved adherence and CD4 cell count response.

In 2013, Maduka et al from Nigeria published a RCT describing the impact of a combination intervention: text messages and monthly one-on-one adherence counseling, also described as motivational interviewing, for four months. Only adults with known poor adherence after at least three months of ART were included. Adherence was measured by self-report, and CD4 cell counts were monitored pre- and post-intervention. The study was short, but well-powered and the randomisation process was clear. The mean ages of the 104 participants were 35-36 years. Pre-intervention CD4 cell counts and adherence were not significantly different between the groups. Both adherence by self-report and CD4 cell count increases were better in the intervention group. Knowledge of drug names and dosing instructions also improved in the intervention group after the 4 counselling sessions. Although this is a high quality study, the impact of the text messages cannot be separated from the counselling intervention.(53)

Text messaging improved viral suppression at 12 months in this good quality study from Kenya.

Mbuagbaw et al presented the Cameroon Mobile Phone SMS trial (CAMPS) in late 2012. This was a RCT, including adults on ART for more than one month. Standard of care is not described, but the intervention included a weekly text containing a variety of interventional messages, and a number to call in need. No reply was required but delivery notifications were monitored. Adherence was measured using self-report (dose recall and visual analogue scale) as well as pharmacy refill data over 6 months, but neither CD4 cell count or viral load were reported [Table 2.4]. The study was well-powered and intention to treat analyses were presented. The randomisation process was sound. Two hundred participants were randomised, with a mean age of 39-41 years. There was no significant improvement in adherence by any of the three measures in the intervention arm [Table 2.5]. Although this study data is of good quality and uses weekly text messages similar to Lester et al, this intervention has no impact in this cohort. (50, 53)

This well-structured study from the Cameroon showed no benefit of weekly text messages on adherence.

Musser wrote a dissertation for the University of Missouri-St. Louis in 2001 which has not yet been published. Data from this study was presented in one of the reviews.(119) This author could not access the dissertation. Adults needing ART, but with suppressed viral loads, in the United States were randomised to receive SoC or text messages for 14 days. Text responses to the messages were required. Details of site and randomisation were not available [Table 2.4]. Adherence was measured using self-report at two weeks; with no biological outcomes reported. These small numbers resulted in wide confidence intervals which crossed unity and so the outcome was not significant.[Table 2.5]. (131)

This unpublished study from the United States showed no benefit of bi-directional text message on adherence over two weeks

The main intervention outcome study for this thesis was published by this author (Orrell et al) in 2015. The manuscript is presented as Chapter three (page 89), but the details have

been added to Tables 2.4 and 2.5 for completeness. Text messaging was used in this study only when a dose was missed, as noted by non-opening of the Wisepill® device. Both adherence and biological outcomes were presented. Randomisation was 1:1 and properly performed. On intention to treat analysis, reminder text messages did not improve overall adherence as measured by this electronic pill-box, nor were virological outcomes improved. (134)

Our RCT from South Africa showed no benefit on adherence or biological outcomes of reminders after a missed dose.

Pop-Eleches et al published the second paper from Kenya showing benefit of text messaging in 2011. Details of this study have also been presented above (page 60). In short, adults who had initiated ART within the previous three months were randomised to receive SoC, daily or weekly text messages. The content of the messages could be short (reminders) or long (reminder and motivational message) [Table 2.4]. Messages did not require a reply. Adherence was monitored using MEMS caps lids on lamivudine bottles. No biological measure was reported. The study was well-structured and the randomisation complex, but clear. Only weekly messaging showed an improvement in MEMS adherence over the SoC. Daily messaging did not improve adherence, and the content of the messaging also did not impact [Table 2.5].(107)

This Kenyan study showed adherence benefit of weekly messaging, with no reply was required.

A recent study published by Sabin et al, from China, used a similar intervention to this author. ART-naïve adults were recruited and stratified at three months into two optimal and sub-optimal adherence strata [Table 2.4]. Each strata was randomised to receive SoC or SoC with reminders 30 minutes after a missed dose. Feedback based on device-generated dosing data was given to each participant at clinic visits. Randomisation was clear and analysis was intention to treat. Adherence was measured electronically using the Wisepill® device and both CD4 cell count and viral load were measured. After a 3 month lead-in period, 119

adults were randomised in two strata. Overall, adherence improved in the intervention arm, with more of an effect seen in those in the sub-optimal adherence arm. However, no improvement in CD4 or VL outcome was noted at 6 months [Table 2.5].(62)

This short RCT from China showed an improvement in adherence, but not biological outcomes, with reminders after missed doses.

The last of the manuscripts for review was by Shet et al in 2014. This RCT was conducted in ART-naïve adults from three HIV outpatient clinics in India. The intervention included a customized automated voice call and a text message. The voice call included a greeting, a health enquiry, and a dosing related question, which required a response through pushing “1” for yes or “2” for no [Table 2.4]. Language and gender of the voice call could be chosen. A neutral pictorial text message was sent four days later. Outcome was measured by tablet return and viral load. Analysis was by intention to treat and the randomisation process was clear. The 631 randomised participants were followed for 24 months. At this point there was no significant difference in adherence by tablet return or risk of virological failure (>400 copies/ml) [Table 2.5]. This is the largest and longest study using mobile phone reminders in the HIV field to date and again does not show benefit from these reminders.(135)

This large study from India showed no adherence or biological benefit of automated calls and text messages over 2 years.

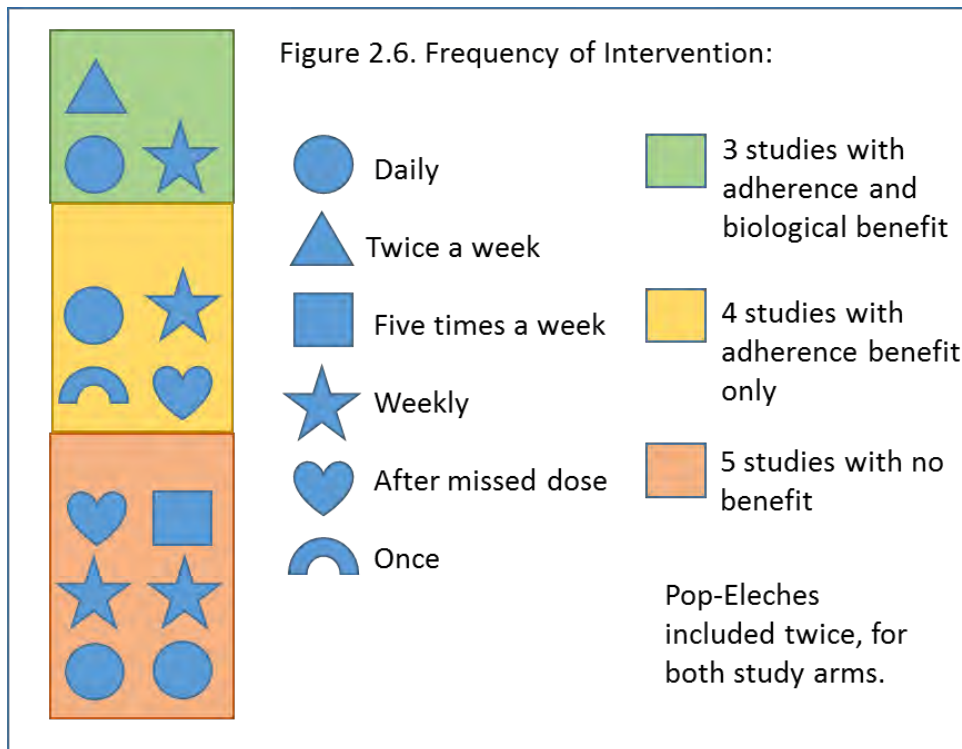
Discussion

The few studies described here have been the subject of multiple reviews. Three examine mobile phone interventions specific to improving ART outcomes: the first was a Cochrane review in 2012 by Horvath et al and included only the Kenyan studies by Lester and Pop-Eleches. (50, 107, 121). The next, by Mbuagbaw et al, in 2013, included the same two studies as well as a third by the review author.(120, 133) A year later Finitsis et al’s review included eight studies (50-52, 107, 131, 133), two of which have not been reviewed here (137, 138) as they used pagers or alarm devices and not mobile phone technology.(119) All three reviews support the use of text messaging, and suggest weekly messages with an

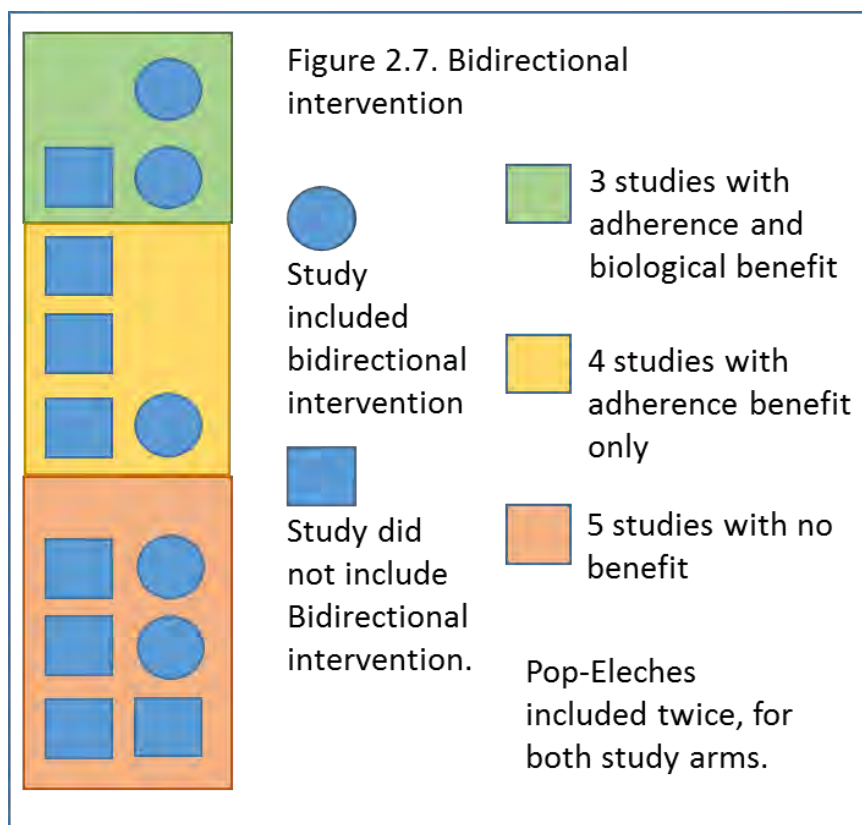
interactive component are optimal. This ties in with the recommendation from Thompson et al, in 2012, that “reminder devices and the use of communication technologies with an interactive component are recommended”.(5)

Another review of adherence methodology by Barnighausen in 2011, also suggested that mobile phone text messages can increase adherence in a sub-Saharan Africa setting. A more recent review, however, is the first to note that while there is strong evidence that such interventions can improve adherence, there are also good studies showing no evidence of benefit.(111)

Of the 12 studies reviewed here, five (42%) showed no benefit of text messages or automated voice calls on either adherence or viral loads. In addition the daily text arm from Pop-Eleches study also showed no benefit. All were randomised studies. Two however, by da Costa and Musser, should perhaps be classified as pilot studies as they were short (4 and 0.5 months respectively) and included fewer than 30 participants each. (52, 131) The other four were substantive studies from Africa or India involving 200 or more adult participants either ART-naïve or within a few months of starting ART. (133-135) In each the messaging and study duration differed. Shet used a combination intervention of a weekly automated call followed by a message over 24 months.(135) Orrell used messages when only dosing was missed over a 12month period and Mbuagbaw used weekly texts over 6 months and Pop-Eleches used daily text messages over a year [Figure 2.6]. (107, 120, 134) Only Shet’s messaging system required participant feedback (bidirectional) [Figure 2.7]. Shet and Orrell reported a lack of benefit on virological outcome, whereas Mbuagbaw did not report a biological response.



Another 4 studies (33%) showed adherence benefit without biological benefit: three did not report any CD4 or VL outcome (Hardy, Bigna, Pop-Eleches) and one reported no improvement in either (Sabin). Two studies included adults noted to be non-adherent, one included naïve adults and the last used a mixed naïve / non-naïve population [Figure 2.8]. Bigna used calls vs text messages vs both and saw no difference between the arms, although all three were better than SoC. The successful intervention in Pop-Eleches used weekly text messages. Hardy sent daily reminders at the time of dosing and Sabin sent reminders only when a dose was missed [Figure 2.6]. Three of the four studies (Bigna, Pop-Eleches, Sabin) did not require participant feedback [Figure 2.7].

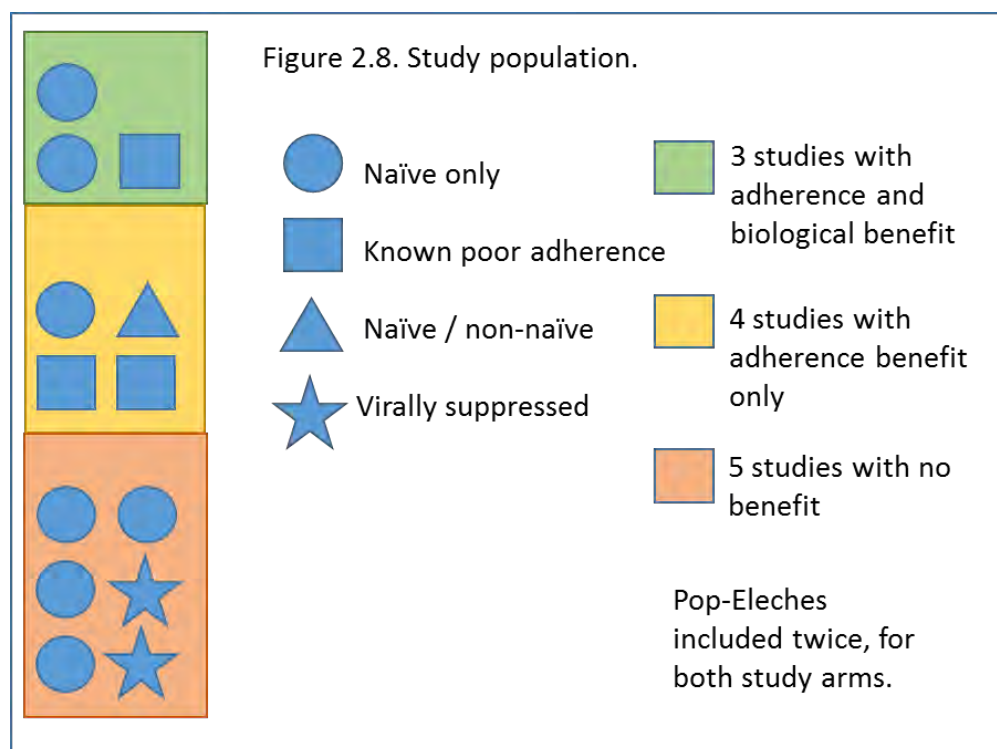


The remaining 3 studies (25%) showed improvement in both adherence and biological outcomes. Both Lester and Maduka's studies had additional human resource intervention: Maduka combined automated twice-weekly text with monthly counseling sessions and Lester had a nurse call people who requested input after the weekly message [Figures 2.6 and 2.7]. Ideka showed benefit from daily dose-linked text messages with no response required. Only Lester and Maduka presented adherence data: both self-report. Maduka selected adults known to be non-adherent and the others included a naïve adult cohort [Figure 2.8]

Outcome measures: While the seven of twelve (58%) studies show some benefit, the remaining five do not. If viral load suppression is taken as the best measure of ART success, then only two studies achieve that goal (17%) [Figure 2.5]. While improving adherence in the early stages of treatment when the viral load is still high is considered especially important, and such interventions might help to create good future tablet taking habits; essentially, improved adherence without biological benefit is likely to have no long-standing value. Here, three studies showing adherence benefit alone did not measure viral load

outcomes, an unfortunate omission which compromises the value of their studies.(51, 107, 139)

Of note, there is no consistent method used to measure adherence, reflecting the lack of clarity about best methods to use [Table 2.5]. Reassuringly, only the oldest study used self-reported adherence as a sole outcome measure.(131) Others that used SR either included an objective measure in addition or included the viral load results.(50-53, 133) In more recent studies there is a positive trend toward the use of electronic devices to monitor adherence.(51, 62, 107, 134) While electronic monitoring is not available in or recommended for programmatic settings at present, the use of best-available methods while conducting research cannot be faulted. (5)



Population: The majority of studies included naïve adults. Bigna et al. examined adult-child pairs, but the intervention remained focused on the adults.(132) No key populations at increased risk of failure were explored. The impact of any intervention will be diluted in a naïve population as the majority those in sub-Saharan cohorts achieve viral suppression at a year in their current programmes anyway.(31, 32, 40) There is only room for the intervention to work in a sub-set of a naïve population. Neither study that selected patients who had already achieved viral suppression noted any benefit, perhaps as this group had

already established reasonable tablet taking patterns.(52, 131) In contrast, all three studies that identified non-adherent adults showed adherence benefit.(51, 53, 62) Here, where the intervention is targeted to those most in need of this type of support, more impact is realized [Figure 2.8].

Intervention: there were seven different types of call/message intervention, reducing in frequency from daily text messages, to five times a week messages, to twice weekly, to weekly [Figure 2.6]. The fewest messages would have been sent in those being reminded of missed doses.(62, 134) Due to concern about message fatigue and the success of weekly messages in Pop-Eleches and Lester's studies more recent studies use weekly messaging, or post-dose reminders [Table 2.5]. However, there were both unsuccessful studies using weekly messages and successful ones using daily messages. Message content does not appear to have alter outcomes. This was measured directly in Pop-Eleches study, (107) but can be seen across the other studies presented here. Five studies used motivational messaging (50, 52, 107, 133, 135), with a range of results [Table 2.5]. The rest used short reminder messages or factual appointment information, also with a range of outcomes from no significance to improving all outcome measures.

2.4. Conclusion.

In 2015, the enthusiastic response to the Kenyan studies may have to be tempered. It cannot be said that all mobile phone interventions have benefit. While the trend toward a positive outcome cannot be doubted, future studies must prove virological as well as adherence benefits, and preferably explore adherence behaviour over a longer duration as expanded ART access in Africa heads into its second decade.

Large numbers of people need care. A method of monitoring adherence to identify those more in need of support within the first few months of ART could reduce burden on ART programmes by allowing early streamlining of care. In our setting, most people who become lost to care in the first year are lost within the first 16 weeks.(134, 140) Those people could be offered a choice from a menu of increased support, based on interventions known to improve adherence e.g. food rations (page 59), educational or counseling interventions (page 50) or text messaging to connect more frequently with their health care team (pages 60 and 71). Similarly, those who do well could also be identified early and the intensity of

their care reduced or offered from a non-clinic venue (page 56).(141) While more research is needed, electronic monitoring and mobile technology should allow us to tailor programmes, if not completely to an individual's needs, at least to an option that most suits that person's requirements.

Chapter three: A randomised controlled trial of real-time electronic adherence monitoring with text message dosing reminders in people starting first-line antiretroviral therapy.

Authors:

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Synopsis:

This manuscript shows the impact that a locally developed real time adherence monitoring device (Wisepill®) with an immediate text message dosing reminders has on adherence and treatment interruptions.

Abstract.

Background: There are conflicting findings about whether mobile phone text message reminders impact on antiretroviral adherence. We hypothesized that text reminders sent when dosing was late would improve adherence and HIV viral suppression.

Methods: ART-naïve participants, from a South African outpatient ART clinic, were randomised to standard of care (SoC, three pre-treatment education sessions), or intervention (SoC and automated text reminders if dosing >30 minutes late). Dosing time was recorded by real-time electronic adherence monitoring devices (EAMD), given to participants at ART start. CD4 cell count and HIV RNA were determined at baseline, 16 and 48 weeks. Primary outcome was cumulative adherence execution by EAMD. HIV-1 viral suppression (<40 copies/ml) at week 48 and count of treatment interruptions (TIs) >72 hours were secondary outcomes. Analysis was by intention to treat (missing=failure). Registration was with the Pan-African Clinical Trials Registry: PACTR201311000641402.

Results: 230 participants were randomly assigned to control (n=115) or intervention (n=115) arms. Median adherence was 82.1% (IQR 56.6-94.6%) in the intervention arm, compared to 80.4% (IQR 52.8-93.8%) for SoC (adjusted odds ratio (aOR) for adherence 1.08, 95%CI:0.77-1.52). Suppressed HIV RNA (<40 copies/ml) occurred in 80 (69.6%) of control and 75 (65.2%) of intervention; aOR for virological failure in intervention arm 0.77, 95%CI:0.42-1.40). In the intervention arm the count of TIs of >72hours was reduced (adjusted incident rate ratio 0.84, 95%CI:0.75-0.94).

Conclusion: Text message reminders linked to late doses detected by real-time adherence monitoring reduced the number of prolonged treatment interruptions, but did not significantly improve adherence or viral suppression.

Introduction.

Increasing numbers of HIV-positive individuals are receiving antiretroviral therapy (ART) in resource limited countries such as South Africa.(6) While early concerns about poor adherence to antiretroviral therapy (ART) among HIV-positive individuals have proved untrue in sub-Saharan Africa (27, 142), treatment expansion to earlier stage disease, however, is creating new adherence challenges, including treatment interruptions and treatment failure.(15, 25, 31, 32) Reliably measuring and improving adherence to first-line therapy is a key component of the 2013 World Health Organisation (WHO) consolidated guidelines. (110)

Electronic adherence monitoring, linked to text message adherence interventions, potentially offers a scalable and accurate adherence monitoring strategy and personalised adherence intervention.(5, 110) As in many low to middle income country settings, South Africa has a well-developed mobile phone network and a high proportion (87%) of the South African population has a mobile phone. (85, 143)

Mobile phone text message reminders have had variable success at improving adherence. Of nine recent randomised controlled (RCT) studies, using text messaging or automated voice messages as an intervention, six have shown some improvement in adherence. (50, 51, 53, 62, 144, 145) Two of these also noted improvement in a biological outcome, either HIV RNA or CD4 cell count. (50, 53) The other three RCTs showed no improvement, either in adherence as measured by self-report or tablet return, or in biological outcome. (52, 133, 135) Many of these studies were of short duration: of 6 months or less.(51-53, 62, 133, 145) Most used messaging in a cyclical manner, usually once or twice weekly, so as not to induce message fatigue. Only one study to date has linked mobile phone text message reminders to real-time detection of missed doses. (62)

We conducted a randomised controlled trial to determine whether text messages triggered by missed doses would improve overall daily adherence execution in ART-naïve South African adults commencing ART. We also examined the impact of the reminder messages on the frequency of treatment interruptions and HIV-1 RNA suppression.

Methods.

Participants and setting:

The Hannan Crusaid Treatment Centre (HCTC) in Gugulethu, Cape Town is a large public sector urban ART outpatient clinic which provides free ART to 7500 HIV-positive individuals. From 2012-2014, multidisciplinary clinic staff included three medical officers, three nurse practitioners, seven clinic-based counsellors and 18 community care workers as described elsewhere.(38) During the period of this study ART-naïve individuals could access ART with clinically advanced disease or a CD4 count of <350 cells/uL according to the South African National ART Guidelines.(10, 146)

Standard of care:

Treatment preparedness: All ART-naïve individuals attending the site received three group treatment preparedness sessions prior to or within the first month of commencing ART. These sessions were delivered by HIV-positive peer counsellors. The information included details about HIV (e.g. what are HIV and a CD4 cell; the importance of the HIV RNA), the ART to be prescribed (including possible side effects, the important of daily adherence and the consequences of poor adherence) as well as advice on healthy living with HIV. All individuals were given a plastic 7-day pill-box on the day they commenced ART.

Antiretroviral therapy: First-line ART in South Africa at the time of the study included tenofovir, lamivudine and efavirenz, given as three separate tablets once a day. Towards the end of the study period in October 2013, a fixed dose combination (FDC) became available, but priority was given to naïve patients entering care and few of the study participants were switched to the FDC during the study. Zidovudine, stavudine, nevirapine and lopinavir in combination with ritonavir were available as alternative agents.

Clinical visits and laboratory sampling: Individuals attended the clinic twice prior to commencing ART and then on day 1 of treatment; after which they attended every four weeks to collect ART and be reviewed by a clinician until week 16. Subsequently they attended every eight weeks to collect ART with clinical review every 16 weeks. A CD4 count

was completed prior to starting treatment and at week 48, and an HIV-1 RNA was drawn at weeks 16 and 48 (and both annually thereafter).(146)

Adherence monitoring: Tablet returns were counted at every visit where ART was dispensed in all participants. Peer counsellors counted the returns and calculated the percentage of tablets taken from the last dispensing to the current dispensing date. This was recorded in the clinical notes prior to the individual seeing the clinician. All participants with tablet count adherence less than 90%, or viral RNA >40 copies/ml, received additional adherence counselling which included an individualised education session with a peer counsellor and monthly dispensing with clinician review until adherence improved.

Missed clinic visits: A tracking list was generated for all missed visits at the end of each month. Individuals were added to this list if they were more than four weeks late for an appointment i.e. no clinic visit, blood draw or ART dispensing had occurred in the last eight weeks for those in the first 16 weeks of therapy, or within the last 12 weeks for those after 16 weeks on ART. All those on the community tracking list were called by a community care worker and, if they could not be contacted by phone, visited at home. This process was repeated every week for up to three attempts. . If tracking was unsuccessful the individual was classified as lost to follow-up.

Study design:

The study was a randomised controlled trial in ART-naïve individuals attending the HCTC, investigating the impact of a real-time electronic adherence monitoring device (EAMD), called Wisepill®, on adherence to ART over 48 weeks. All participants received the EAMD on study entry, in exchange for the plastic pillbox given by the clinic on ART commencement, and were randomised to either: 1) standard of care (described above, with Wisepill device in lieu of the pillbox) or 2) reminder text messages linked to non-opening of the device.

Inclusion and exclusion criteria: Participants were recruited from ART-naïve adults and adolescents (≥15years) commencing treatment at the HCTC. Possession of their own mobile phone was required for inclusion into the study. Written informed consent or, in the case of participants younger than 18 years, assent, was given by each participant. Entry into the study was offered consecutively to all eligible participants presenting to the clinic.

Study visits and sampling: All participants received care at the HCTC as per the standard of care detailed above. (25, 33) Participants were seen by study staff, in addition to their clinic visit, at their first visit to the clinic (screening visit), their first day of ART (day 1, baseline visit), and at weeks 16, 32 and 48 on treatment. Study staff included a study coordinator and three research assistants, who collected the study data and completed the questionnaires with each participant, but who offered no clinical care or adherence support. Study visits were timed to coincide with booked clinic visits to minimise inconvenience to the participant. Participants were reimbursed for local travel (R20 or ~US\$2) at each study visit and in addition, for the three on-treatment study visits (weeks 16, 32 and 48), were given a gift of a T-shirt, bag or mug valued at R80 (~US\$8) to compensate them for their time.

Demographic and psychosocial details, including age, gender, weight, height, anxiety and depression scores using the 14 question Hospital Anxiety and Depression Score (HADS), alcohol abuse as assessed by the four-question CAGE score (Have you ever felt you should **C**ut down on your drinking; have people **A**nnoyed you by criticizing your drinking; have you ever felt bad or **G**uilty about your drinking; and, have you ever had a drink first thing in the morning to steady your nerves or to get rid of a hangover (**E**ye opener?))(147), and details of any friends or family to whom they had disclosed their HIV status were collected at the screening visit. (148, 149) Non-disclosure was defined as not having revealed his/her HIV status to anyone outside of the clinic.

Blood was drawn by the study coordinator or the clinic nurse for CD4 cell count (FACS Count™, Beckton Dickinson, NJ, USA) and HIV-1 RNA (HIV-1 RNA 3.0 assay®, Bayer Healthcare, Leverkusen, Germany), at screening, weeks 16 and 48. Baseline HIV RNA and CD4 cell count at week 16 were the only samples drawn in addition to those routinely completed by the clinic. Prescribed ART and WHO clinical stage were recorded at the baseline visit. Participant's eligibility for the study was confirmed and randomisation occurred thereafter.

Self-reported three-day recall of adherence, questions on EAMD acceptability, disclosure status and the CAGE questionnaire were asked by the study counsellors at weeks 16 and 48. The 14-question HADS was completed again at week 48. Weight was measured and current

ART confirmed at all visits. At all visits mobile phone numbers were confirmed and note was made of participants on TB treatment or who were pregnant.

Throughout the study, clinic adherence monitoring and tracing after a missed visit continued as per standard of care. The EAMD was returned and exchanged for a standard pill box at the end of study visit, 4 weeks after the week 48 visit. Participants were reimbursed R150 (~US\$15) at this visit.

Randomisation: Participants were randomized 1:1 to control and intervention arms. Allocation to study arm was concealed in sealed individual opaque envelopes, which were numbered from 1 to 230 and opened consecutively after a participant met study entry criteria. The random number sequence and envelopes were generated off-site. The envelopes were opened by the study nurse, blinded to the allocation, on-site. Staff (both study and clinic) and participants were not masked to arm allocation after randomisation.

Adherence monitoring: The Wisepill® device is a locally-produced electronic device the size of a mobile phone which can store up to a week of medication in a seven compartment pill box. (150) This EAMD has been used in other resource-limited settings to measure adherence. In these studies the device was shown to be reliable, and adherence by EAMD to be significantly associated with viral suppression.(60, 63) All participants received a Wisepill® device and were given additional internal pill boxes with instruction on refilling and replacing these weekly. On opening, a signal was sent in real time via the wireless telecommunications network to a secure central computer in Somerset West, Cape Town.

Each EAMD gave a daily “heartbeat” signalling that it was still on-line and checking the battery voltage. Charged batteries lasted for about three months. Each participant was given a wall charger to use at home as well as the option of bringing their device to the clinic for recharging. If the “heartbeat” showed a low voltage, a message was sent to the participant reminding them to charge the device: “Sicela utshaje ibhokisi yakho yeepilisi okanje uyizise ekliniki sikutshajele. Please charge your Wisepill box or bring to the clinic so we can charge it for you”. In addition, a weekly low battery report was sent to the study co-ordinator, who called these participants and reminded to charge their EAMD.

Intervention: All participant's preferred daily dosing time was recorded in the Wisepill® system. Intervention participants received a text message if the device was not opened within 30 minutes of the scheduled dosing time. This window was chosen by the participants as they did not want to be woken by a later message (due to evening dosing of efavirenz regimens). The first five participants randomised were asked to construct a simple message that would remind them to take their tablets, but not disclose their HIV-status to others at home or in the community. These message options were then made available for the rest of the cohort, in either English or Xhosa. Once each participant in the intervention arm had chosen a message, they received the same message throughout the study when their dosing was late. Messages included "Have you forgotten something?" (Awulibelanga nto?), "Just take it!" (Yithathe!), "Wake up" (Vuka!), "It's 8 o'clock! (Ngu 8 o'clock!) or their study number (e.g.XX9999). In addition, for the intervention participants, a report of on-time, late and missed doses over the previous 4 months was placed in their clinical folder for the ART clinician to review every 16 weeks during the study.

Outcomes and statistical analysis: Participants were classified by the following retention in care outcomes prior to calculating the primary adherence and virologic outcomes:

- *Completed study:* these participants were in care at the clinic at the time of the end of study visit.
- *Transfer out:* some participants requested a transfer to another ART clinic. Transfer out date was recorded as the last date the participant attended the HCTC. These participants were censored at transfer out date.
- *Death:* Deaths were ascertained from clinical notes or from discussion with the family. Date of death is usually clear, but if not, date of last contact with the clinic was used. These participants were censored at date of death.
- *Loss to follow-up (LTFU):* Participants were considered LTFU if they had not attended the clinic, had blood drawn or collected medication for more than 12 weeks. In addition they could not be traced, as per standard of care for missed visits, and were not known to have transferred out or to have died. The date of LTFU was taken as the last date they attended the clinic. For per protocol analyses, these participants were censored at their LTFU date. For intention to treat analyses these participants were censored at their calculated week

48 date, i.e. the date of randomisation plus 336 days. EAMD opening data recorded after last date in clinic and before calculated week 48 date were included in the analysis.

The primary outcome was adherence execution as measured by the EAMD. Adherence execution was calculated by the number of days the container was opened over the number of days in the period in care (for those who completed the study, transferred out or who died); and for the period from randomisation to calculated week 48 for those LTFU. Multiple openings on one day were truncated at 100%. Days without battery charge were censored.

The adherence data were modelled both as categorical and continuous variables. A fractional logit model (continuous data assessed using a generalised linear model with a logit link) was used for the continuous data and a logistic regression model using a logit transformation was used for the categorical data. The cut-off for the categorical adherence data was informed by the median of the continuous data. We used an intention to treat approach for this primary outcome.

Retention in care, virological suppression and number of >72 hour treatment interruptions were secondary outcomes. Those who completed the study or who were transferred to care elsewhere were considered retained in care. Those who died or were lost to follow-up were considered lost to care. The impact of the intervention on retention in care was modelled using a multinomial logistic regression model.

The impact of the intervention on virological outcomes (both to <40 copies/ml and <400 copies/ml) was modelled using linear mixed effect models. The impact of the intervention on the number of treatment interruptions was modelled using Poisson regression.

Treatment interruptions were defined as interruptions of 72 hours or longer, i.e. 3 or more missed doses, as it has previously been shown that sustained missing of doses has more impact on virological outcome than single missed doses, with each day beyond two missed days increasing the risk of virological breakthrough.⁽¹⁷⁾

Data were analysed using Stata 13.0 (Stata Corporation, College Station, USA). Descriptive statistics were used to summarise the baseline characteristics of the participant group. The Chi-squared test was used to compare proportions and the two-sample t-test to compare continuous variables. Variables were pre-selected for inclusion in the multivariate analyses. .

Role of funding source:

The sponsors of the study had no role in the design and implementation of this study, nor in manuscript preparation. All authors had full access to the study data. CO developed the initial manuscript and all authors approved the submission.

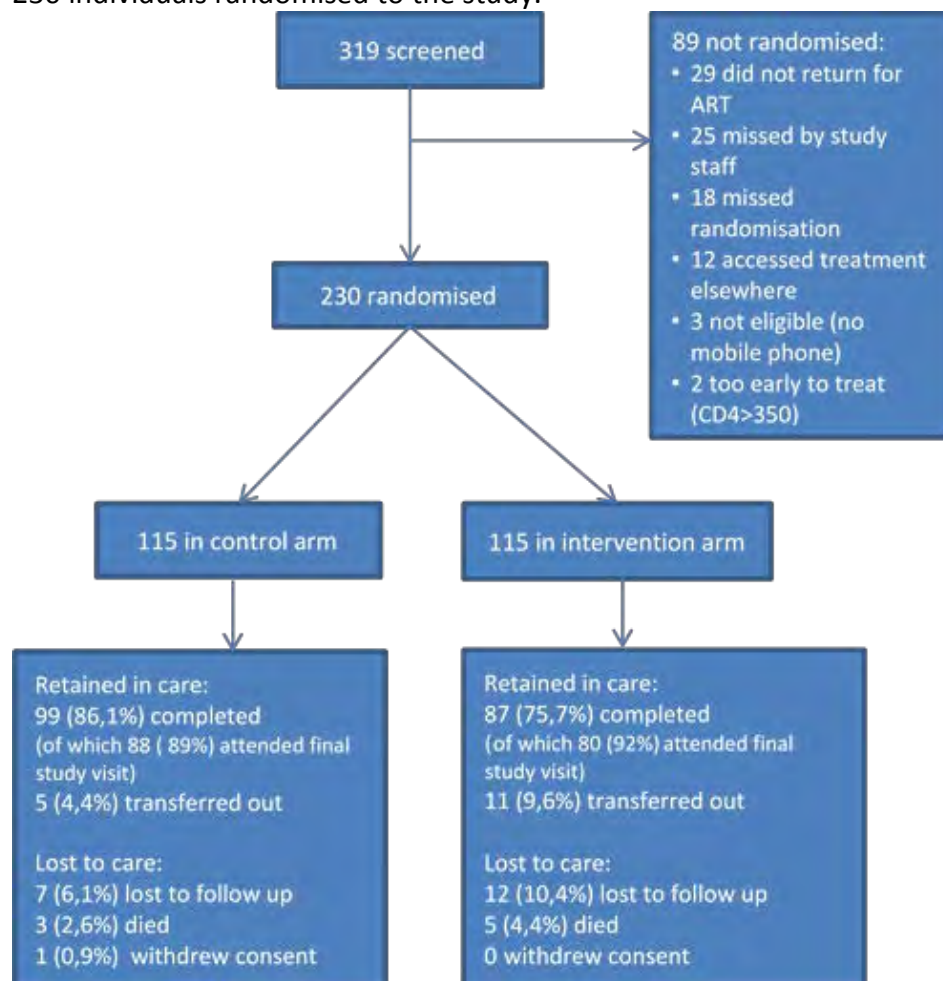
Ethical approval:

The University of Cape Town Faculty of Health Science Research Ethics Committee gave approval to conduct this study. Each participant provided written informed consent or assent. The trial was registered in the Pan African Clinical Trials Registry, number PACTR201311000641402.

Results.

Between July 2012 and April 2013, 319 participants were screened and 230 were randomised. Eighty-nine people were not randomised, due to the reasons given in Figure 3.1. Baseline characteristics were similar between those who randomised and those who were not, as well as similar by randomisation arm (Table 3.1). The mean age of the enrolled cohort was 34.5 (± 9.1) years, with 150 (65.2%) women. Median CD4 count at start was 225.5 (IQR 133-287) cells/mm³. All participants had detectable HIV RNA at baseline. There was no significant difference in either HADS scores or the CAGE score at baseline by randomisation arm.

Figure 3.1: Flow diagram describing the outcome of the 319 individuals screened and the 230 individuals randomised to the study.



Most participants were started on efavirenz-based regimens (n=228, 99.1%) and two on nevirapine-based regimens. All ART included lamivudine. The majority (n=225, 97.8%) were started on tenofovir as the second nucleoside reverse transcriptase inhibitor (NRTI). Depression (n=74, 32.1%), anxiety (n=89, 38.7%) and alcoholism (n=35, 15.2%) were highly prevalent. Most participants had disclosed their status to at least one other person (n=219, 95.2%).

Table 3.1 – Baseline demographic, clinical, treatment and psycho-social characteristics of participants by arm.

	Control	Intervention	p-value
N	115	115	
Female sex: n(%)	77 (67.0)	73 (63.5)	0.678
Age in years: mean (sd)	34.3 (9.0)	34.6 (9.2)	0.779
Height (cm): mean (sd)	164.0 (8.6)	164.1 (8.6)	0.932
Weight (kg): median (IQR)	68.4 (60.1-79.6)	67.0 (56.1-80.0)	0.320
WHO stage: n(%)			0.946
1	42 (36.5)	42 (36.5)	
2	24 (20.9)	23 (20.0)	
3	36 (31.3)	39 (33.9)	
4	13 (11.3)	11 (9.6)	
CD4 count: median (IQR)	229 (136-292)	225 (121-283)	0.543
Log HIV RNA (copies/ml): median (IQR)	4.8 (4.4-5.4)	5.0 (4.5-5.4)	0.324
Range of HIV RNA at baseline (minimum – maximum copies/ml)	109 – 1 481 459	1 021 – 2 381 184	
NNRTI at start: n(%)			0.498
Efavirenz	115 (100.0)	113 (98.3)	
Nevirapine	0 (0.0)	2 (1.7)	
NRTI at start*: n(%)			0.361
Tenofovir	114 (99.1)	111 (96.5)	
Zidovudine	1 (0.9)	3 (2.6)	
Stavudine	0 (0.0)	1 (0.9)	
HADS <u>depression</u> score of 8 or above (borderline or case)**	43 (37.4)	31 (27.0)	0.09
HADS <u>anxiety</u> score of 8 or above (borderline or case)**	51 (44.3)	38 (33.0)	0.08
Non-disclosure	5 (4.4)	6 (5.2)	0.757
CAGE ≥2	20 (17.4)	15 (13.0)	0.359

* All were taking lamivudine or emtricitabine in addition.

** Hospital Anxiety and Depression Score.

The 230 participants were in care for a median of 380 days (IQR 359-414 days). Only one person withdrew consent during the study. The majority (n=186, 80.9%) remained in care at

the site and most also completed the study visits, as noted in Figure 3.1; or were transferred to care at another site (n=16, 6.9%). Nineteen participants (8.3%) were lost to follow up and eight (3.5%) died.

Primary outcome - adherence:

At week 48, there was no difference in median adherence by self-report or tablet return by arm. By tablet return, the median adherence was 100% in both arms (IQR 95-110% in the intervention arm and 94-100% in the control arm). By self-report, median adherence was 100% in both arms (IQR 100-100% in both arms).

Median adherence by EAMD was 82.1% (IQR 56.6-94.6%) in the intervention arm and, 80.4% (IQR 52.8-93.8%) in the control arm. This difference was not significant either when modelled as a continuous variable (Table 3.2) or as a categorical variable in a logistic regression model, using adherence >80% as the cut-off value (model not shown). Age was the only variable significantly associated with adherence execution (Table 3.2). The number of pills taken, relative to the number of pills not taken, increased by 27% for each 10 year increase in age: OR 1.27 (95%CI 1.05-1.52). Gender, non-disclosure, anxiety and depression scores, as well as baseline CD4 cell count did not impact on adherence execution in this model.

Table 3.2. Generalised linear model (GLM) of cumulative adherence by EAMD over time on study. (Data from 230 participants included in the model)

Adherence	Odds Ratio	Std. Error	p-value	95% Confidence Interval
Intervention arm	1.08	0.19	0.642	0.77 - 1.52
Age*	1.02	0.01	0.014	1.00 - 1.04
Anxiety score >8	1.05	0.19	0.797	0.74 - 1.49
Depression score >8	0.74	0.14	0.100	0.51 - 1.06
CD4	1.00	0.00	0.699	1.00 - 1.01
Male sex	0.96	0.17	0.802	0.68 - 1.34
Non-disclosure	0.72	0.30	0.368	0.32 - 1.63
Screen CAGE ≥2	1.05	0.45	0.819	0.67 - 1.67

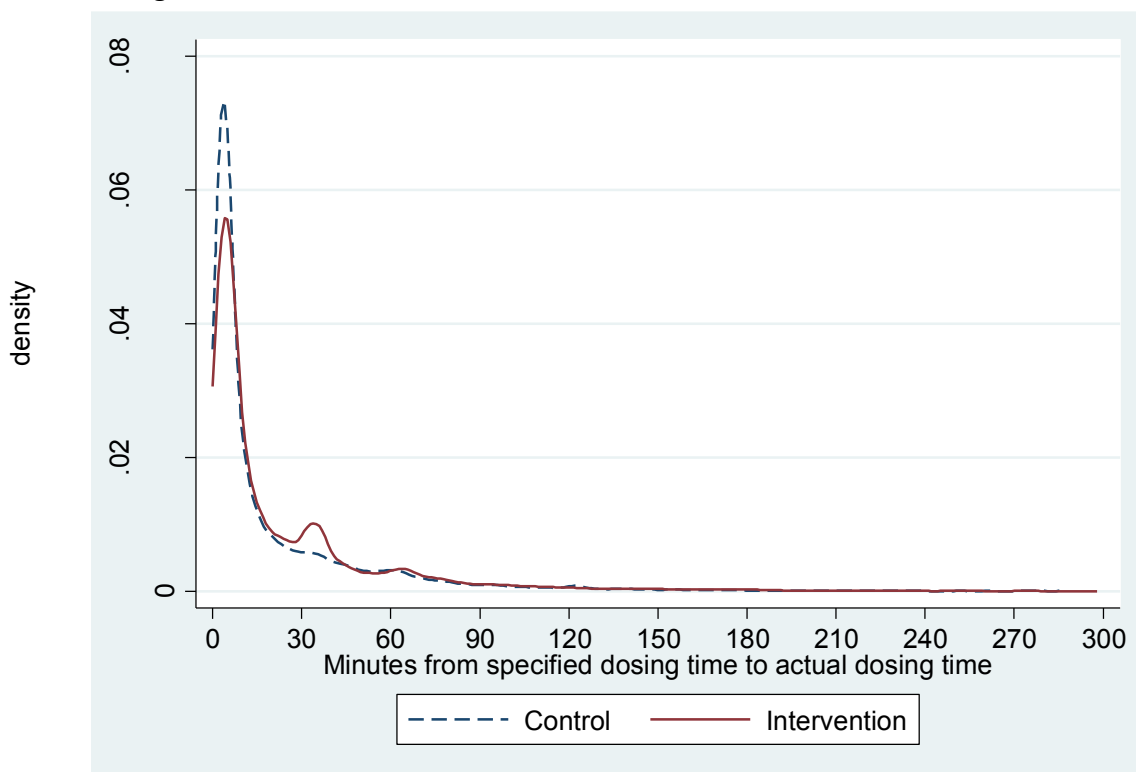
*The number of pills taken, relative to the number of pills not taken, increases by 27% for each 10 year increase in age: OR 1.27 (95%CI 1.05-1.52).

EAMD data revealed there were 82311 participant dosing days recorded; 40188 were in the intervention arm 42123 in the control arm. Of these, 8362 (10.1%) were dead battery days. Dead battery days were evenly distributed by arm.

In the intervention arm 19142 text messages were sent to 114 individuals, equating to 47.6% of doses not being taken within 30 minutes of the specified dosing time. The most

popular message was “Have you forgotten something?” in English, chosen by 31 (26.9%) participants; followed by “Vuka” chosen by 27 (23.5%). There was no difference in adherence execution by message. After the message, on 5340 occasions (13.2%) the EAMD was opened, in a median time of 22 minutes (IQR 6-47 minutes). There was no evidence of reminder fatigue by weeks on study. In the control arm 23255 (55.2%) of doses were taken on time, and on 4069 occasions (9.7%) dosing was taken later that day, without reminder. Figure 3.2 shows the median time (in minutes) from the dosing time specified by each participant to the actual time of dosing. The density on the y-axis reflects the probability or frequency of the dose being taken at each time point. More people in the control arm took their tablet on time while a subset of those in the intervention arm (solid line) waited for the text message at 30 minutes post-specified dosing time before dosing.

Figure 3.2: Graph showing the median time (in minutes) from the dosing time specified by each participant to the actual time of dosing. The area under the curve equals to one, and the density (y-axis) shows the probability of patients taking their dose at that time point. More people in the control arm, (dotted line) dose on time. In the intervention arm (solid line) the effect of individuals waiting for the text message at 30 minutes after their specified dosing time can be seen.



Secondary outcomes – HIV RNA:

At week 16, 198 of 230 (86%) participants had a HIV RNA available. 143 (72%) achieved a HIV RNA of <40 copies/ml: 73 of 97 (75.3%) in the intervention arm and 70 of 101 (69.3%) in the control arm. At week 48, of the 182 participants remaining in care, 155 (85.2%) had a HIV RNA of <40 copies/ml: 75 of 86 (87.2%) in the intervention arm and 80 of 96 (83.3%) in the control arm. There were 32 missing values at week 16 and 48 missing values at week 48. Using intention to treat analysis, where the missing values equalled failure, a mixed effects model showed no difference in the odds of virological failure (>40 copies/ml) in the intervention arm (OR 0.77, CI 0.41-1.4, p=0.393). Only a baseline HIV RNA of >5 log copies/ml significantly increased the chance of virological failure (OR 2.03, CI 1.1-3.9, p=0.034). The model is shown in Table 3.3. There was similarly no difference in virological outcome by arm using per protocol analysis where missing values were kept as missing values.

Table 3.3: Linear Mixed effect model for virological failure (VL>40copies/ml at weeks 16 and 48). Missing results equalled failure.

HIV RNA > 40 copies/ml	OR	Std. Error	p-value	95% Confidence Interval
Intervention arm	0.77	0.23	0.393	0.42 - 1.40
BMI*	0.96	0.03	0.195	0.91 - 1.02
B-I VL >5 log copies/ml	2.03	0.68	0.034	1.05 - 3.91
Age	0.97	0.02	0.143	0.94 - 1.01
Male sex	0.91	0.33	0.800	0.45 - 1.86
CD4 count	0.99	0.00	0.187	0.99 - 1.00
Week 48	0.67	0.17	0.109	0.41 - 1.09

* BMI = body mass index

Secondary outcomes – treatment interruptions (TIs):

The median duration of treatment interruptions was 8 (IQR 5-15) days, with no difference by study arm. However, using a Poisson regression model for estimation of incidence rate ratios (IRR), the count of treatment interruptions of >72 hours in the intervention arm was significantly less than in the control (Table 3.4). This was seen in both univariate analysis, where there was an 18% reduction in the count of these TIs in the intervention arm (IRR 0.82, 95%CI 0.74-0.92), and in multivariate analysis (aIRR 0.84, 95%CI 0.75 – 0.94; p=0.003), as shown in Table 4, compared to control. Additional factors associated with TIs were age, which was protective. A 14% reduction in frequency of TIs was noted for each 10 year increase in age (aIRR 0.86, 95%CI 0.80-0.92). There was a 36% increase in the frequency of

TIs for those with a HADS depression score >8 (aIRR 1.36, 95%CI 1.21-1.53) and a 30% increased frequency of TIs in men compared to women (aIRR 1.3, 95%CI 1.15-1.47).

Table 3.4: Poisson regression model for count of treatment interruptions (ITT, 230 participants used in the model).

Count of TI >72hours	IRR	Std. Error	p value	95% Confidence Interval
Intervention arm	0.84	0.049	0.003	0.75 - 0.94
Age*	0.99	0.003	0.000	0.98 - 0.99
Baseline CD4	0.99	0.000	0.616	0.99 - 1.00
Male sex	1.30	0.079	0.000	1.15 - 1.47
Anxiety score >8	0.96	0.058	0.466	0.85 - 1.08
Depression score >8	1.36	0.083	0.000	1.21 - 1.53
Screen CAGE ≥2		1.08	0.087	0.331
Non-disclosure		1.19	0.163	0.194

* The relative count of TI for each 10 year increase in age decreased by 14%: aIRR 1.86 (95%CI 0.80-0.92)

Secondary outcomes – retention in care:

The characteristics of those who died, were lost to follow-up and transferred out, as in Figure 3.1, were compared to those who had completed the study using a multinomial logistic regression model (model not shown). There was no difference between those who died, were lost to follow-up or transferred out and the completed group by intervention arm.

Discussion.

Our randomised controlled trial found that the use of a novel, wireless, electronic adherence monitoring device, which generated a text message reminder for device openings >30 minutes late, significantly reduced the frequency of treatment interruptions longer than 72 hours, but had no effect on overall adherence execution, retention in care, or HIV RNA suppression among ART-naïve individuals attending a South African community clinic. Time from message to dose ingestion did not fatigue over the study, suggesting durability of the intervention effect. However, participants in the intervention arm were more likely to take their dose outside of the 30 minute dosing window, suggesting that they relied on the intervention to remind them to dose.

The intervention significantly reduced the frequency of treatment interruptions of over 72 hours, which was a pre-specified endpoint. This is an important finding as treatment interruptions >72 hours have been shown to be a significant cause of virologic failure and acquisition of drug resistance independent of average overall adherence among participants receiving NNRTI treatment. (17, 43, 151) The intervention altered the pattern of adherence behaviour, changing the frequency of longer treatment interruptions, despite similar median adherence. Text message reminders made it more likely that participants on the intervention arm would dose at least every 72 hours, while those in the control arm had longer gaps in dosing.

The median duration of treatment interruptions was 8 days, with an IQR of 5-15 days. People on NNRTI-based regimens, like the participants in our study, have a 50% chance of viral rebound after a 14 day interruption, although this risk of failure decreases with the duration of viral suppression before the interruption occurs. (17, 152, 153) It is likely that the treatment interruptions in our study were either too short or occurred after sufficient viral suppression to generate a difference in viral suppression at week 48. (17)

Age, gender and depression were significantly linked with an increased frequency of treatment interruptions. Specific populations, namely younger people, men and those with symptoms of depression, might benefit from focussed adherence interventions. Younger people were also more likely to have poor adherence execution, and to be lost to care.

Further exploration of simple adherence interventions, such as the one used in this study would be warranted in these young people.

Transfers to care at other clinics (6.9%), and losses to care (8.2%) were similar to what has previously been reported at this site.(40, 154). Eight people (3.5%) died; a smaller proportion than noted in the same earlier studies, likely reflecting earlier entry to care with the expansion of the South African ART programme and raise in baseline CD4 cell count inclusion criteria (from 200 to 350 cells/mm³) in August 2011. (146) The intervention in this study did not impact on these losses. Those who were lost to care were younger than those who remained in care and were more likely not to have disclosed their HIV status to anyone else.

Our study has several strengths including objective monitoring of adherence, 12 month follow-up, and use of HIV-1 RNA as an outcome. One potential limitation of the study is that adherence in this cohort is already excellent.(38) All participants received a higher level of adherence support at our clinic than is routine in most settings, including thorough treatment preparedness, regular clinic pill counts and extra support through education and home visits should adherence flag. All of these interventions are known to improve adherence. (155, 156). A further potential limitation is that we sent our text messages to the participant's own mobile phones and, despite regular confirmation of telephone numbers, other than the increased numbers of people dosing at the time the message was sent (Figure 2), we do not have data to confirm that all messages were actually received.

In summary, our study found that electronic monitoring with text reminders for late doses reduced the frequency of treatment interruptions without a difference in overall adherence or HIV RNA suppression in the context of high levels of adherence support. While systematic reviews and meta-analyses have concluded that text messaging is a potential option to support adherence to antiretroviral therapy, (5, 111, 112, 119, 120, 157, 158) future studies are needed to determine best timing of the reminders and whether the level of adherence support supplied by electronic monitoring can replace intensive counselling linked with home visits in this population.

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Chapter four: Simplifying HIV Cohort Monitoring - pharmacy stock records minimise resources necessary to determine retention in care.

Authors:

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Publication status:

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Synopsis:

This short report illustrates how an existing locally developed pharmacy database (iDART) is better used to monitor cohort retention than standard cohort monitoring processes.

Abstract.

Introduction: Monitoring of antiretroviral therapy (ART) delivery scale up is operationally complex, yet crucial to on-going programmatic success. Current cohort monitoring systems (paper or electronic) can be unwieldy. Pharmacy dispensing reports may provide quick and cost-effective methods of determining numbers starting treatment and retained in care.

Methods: Reports of the number of individuals in ART care generated quarterly over one calendar year (July 2010 to June 2011) from the Access-based ART cohort database at a resource-poor clinic in South Africa (cohort report) were compared to numbers in care generated from the electronic dispensing system used in the clinic over the same time period (dispensing system report). Staff time taken to generate the reports with both systems was estimated.

Results: The cohort reports at the end of September and December 2010, March and June 2011 showed a linear increase in numbers on therapy with 814, 875, 903 and 928 individuals in care at the end of each quarter respectively. By dispensing system reports, the number of people per quarter on ART was 779, 829, 852 and 886. These numbers were largely within an acceptable margin of 5% of each other. Staff time to generate the cohort report amounted to 30.9 hours per month, compared to 0.2 hours a month for the dispensing system report.

Conclusion: Electronic dispensing system reports are easy to generate and comparable to clinic cohort reports when used to identify individuals remaining in care. Dispensing reports are much more time efficient.

Background.

Monitoring of the rapid scale up of antiretroviral therapy (ART) delivery in resource-poor countries is complex, yet crucial.⁽¹⁵⁹⁾ The primary purpose of determining how many individuals commenced and remain on ART over a particular period is for forecasting ART supplies and service. These data provide a measure for judging progress and determining where funds are being used effectively. The number of people remaining on therapy is an indicator of the United Nations General Assembly Special Session report (UNGASS). Another purpose of these data is for clinical monitoring of individuals. Identifying those remaining on therapy by necessity identifies those who are not, thus allowing for those who are lost-to-follow-up to be recalled.

Monitoring systems vary from site to site, by resources available and local expertise. Paper-based systems cannot work efficiently with large patient numbers. Electronic clinical data capture systems are being used in some Sub-Saharan African ART sites, including South Africa and Malawi, but consume clinical time and require infrastructure.^(160, 161) Alternatively, pharmacy dispensing records could provide an accurate, quick and cost effective record of drug collection and hence retention in care over a defined time period.^(57, 84) Coupling the clinical monitoring system to that for drug stock levels reduces duplication and streamlines the required reporting processes.

The aim of this study was to determine whether the pharmacy record can provide an adequate estimate of the number of patients commencing and retained on ART compared to the currently used clinic cohort reports.

Methods.

Setting:

Masiphumelele is a small community of 17 000 individuals, with an HIV prevalence of 25%.(162) Masiphumelele has one clinic that offers primary care services. Patients requiring ART were supported by a multi-disciplinary team. ART was dispensed according to the South African National ART guidelines, a non-nucleoside reverse transcriptase inhibitor (NNRTI)-based first-line and a protease inhibitor-based second-line regimen.(146, 163) This service has been described previously both in terms of staff providing care and losses to care over time.(37, 81)

Data collection:

Clinic cohort reports: clinicians completed a data capture form for each patient visit, which was transferred weekly to the University of Cape Town for clerks to enter into an Access® database. A data manager generated monthly and quarterly reports through pre-prepared queries detailing individuals commencing ART and those retained in care. Another list of those not retained in care or “lost-to-follow-up” was generated to commence the recall process.

Four consecutive clinic cohort quarterly reports were analysed from the ART Access® database. The number of patients commencing ART and those remaining on therapy at the end of each quarter were calculated from the difference between the number of patients ever started and those known to have died, transferred-out and defaulted by the end of each quarter. For this study, the clinic cohort reports were considered the gold standard.

Pharmacy reports: Pharmacy records were kept using the Intelligent Dispensing of ART (iDART) system, a pharmacy application developed from open source software. iDART recorded each ART bottle’s bar code as it was scanned out and linked it to the individual receiving the drug.

A pharmacist or pharmacy assistant generated two automated reports from the iDART system. The clinic indicator report included the total number of individuals initiated on ART as well as the total number of individuals seen per quarter. Each of these numbers was

compared as a simple ratio with the clinic cohort report of numbers commenced and remaining on therapy at the end of the same four consecutive quarters.

The ART drug usage report, reported stock consumption i.e. the number of bottles of each antiretroviral dispensed in the reporting period. As each ART bottle contains 30 days' supply, this report was used to calculate the number of months of medication dispensed per individual by totalling the number of bottles of efavirenz, nevirapine and lopinavir/ritonavir dispensed per quarter (each individual will only be taking one of these at a time) and dividing by the number of individuals seen during that reporting period.

Comparative analysis:

Data are presented as numbers and proportions. Clinic based and pharmacy based records were compared using simple ratios to compare whether patient retention on therapy as determined by pharmacy records was within our defined acceptable limit ($\pm 5\%$) of patient retention as determined by clinic cohort analysis.

Ethical clearance:

Ethics approval for collection of clinical data from individuals on ART at Masiphumelele has been received from the University of Cape Town Research Ethics Committee.

Results.

Clinic cohort report results: Patient data collected from the Masiphumelele quarterly reports at the end of September 2010, December 2010, March 2011 and June 2011 showed an increase in numbers on therapy with 814, 875, 903 and 928 adults and children cumulatively in care at the end of each quarter respectively (Table 4.1). Sixty-seven, 63, 63 and 52 individuals commenced therapy over the same four quarters.

Dispensing system report results: The numbers of individuals who were collecting ART per quarter by iDART clinic indicator report was 779, 829, 852 and 886. Seventy-six, 75, 69 and 52 commenced treatment per quarter (Table 4.1).

Table 4.1: Comparing clinic cohort reports and iDART clinic indicator reports:

a. Total adults and children commencing antiretroviral therapy per quarter.

	01Jul10 to 30Sep10		01Oct10 to 31Dec10		01Jan11 to 31Mar11		01Apr11 to 30Jun11	
	Adult	Child	Adult	Child	Adult	Child	Adult	Child
Clinic cohort report	65	2	60	3	60	3	50	2
iDART clinic indicator report	74	2	69	6	66	3	50	2
Ratio (iDART/clinic)	1.13	-	1.19	-	1.09	-	1.0	-

b. Total adults and children retained on antiretroviral therapy per quarter.

	01Jul10 to 30Sep10		01Oct10 to 31Dec10		01Jan11 to 31Mar11		01Apr11 to 30Jun11	
	Adult	Child	Adult	Child	Adult	Child	Adult	Child
Clinic cohort report	768	46	826	49	854	49	893	49
iDART clinic indicator report	737	42	784	45	807	45	846	43
Ratio (iDART/clinic)	0.96	-	0.95	-	0.94	-	0.95	-

Comparison of clinic cohort and dispensing system reports is presented in Table 4.1. For each quarter iDART overestimated numbers starting therapy by up to 13% and underestimated numbers retained in care by up to 6%. For the first, second and fourth quarters, the numbers retained on ART by clinic cohort report correlated well with the dispensing report of individuals collecting drugs (within 5%). For the third quarter the totals correlated less well.

As each bottle contains 1 month of medication, the expected number of bottles an adult should receive per quarter would be three, as seen in the first (3.14 per adult) and fourth (3.17 per adult) quarters described. In the second quarter, each adult received an increased average of 3.8 bottles of either NNRTI or PI and in the third, a reduced average of 2.86 bottles.

Discussion.

This report is part of the first study in Southern Africa to explore the practicality of using pharmacy dispensing records to estimate the number retained in ART care per quarter in a resource-poor setting. The pharmacy dispensing report of individuals collecting ART closely reflected the clinic cohort reports, but in two of the four quarters monitored, the stock dispensed was either more or less than expected.

The number of people on ART at the end of the quarter as per the clinic cohort report might be expected to differ from that of the dispensing reports. As prescriptions were generated at the weekly multidisciplinary meeting where all pre-treatment individuals were discussed, treatment start is captured easily, though there may be a lag time from dispensing ART to the capturing of that information in the clinical database, reflected as more individuals starting therapy per quarter in Table 4.1. Losses to care (deaths, loss-to-follow-up and transfers-out) are more difficult to capture in the clinic cohort report, while being immediately reflected in the dispensing reports as those individuals do not collect ART. While there was an active clinical tracing process, at the date of any report there may be individuals lost-to-follow-up or who have died who have not yet been identified as such, so giving increased numbers in care by clinic cohort report, again reflected in Table 1, where the numbers were slightly more than, but within 6% of, the dispensing report in all four quarters.

While the existing iDART system at Masiphumelele clinic cannot initiate a tracing process for those who miss their ART collection date, this is something feasible for the iDART system and is being explored in other South African clinical settings. This would allow coupling of the current clinical and dispensing reporting systems and reduce duplication of effort.

In the October to December quarter, more drugs were dispensed than expected (3.80 bottles per person) and in the January to March quarter less drugs were dispensed than expected (2.85 bottles per person). This reflected the migratory process in greater Cape Town area, where many go home to their province of origin over the holiday season. Many of these people will not seek care while away and interrupt ART. To pre-empt this, ART clinics, including Masiphumelele, over-dispense in the months prior to December. This, and

more loss-to-follow-up as people fail to return, results in the under-dispensing noted in the first quarter of the year.

There are weaknesses in this report. Assessment of time taken to complete each report was not accurately assessed, but many more staff are required to generate the clinic cohort report than the pharmacy report. There may also be errors in the dispensing process such as failure to scan the bar code at the time of dispensing, which would impact on numbers in the dispensing reports.

Conclusion.

Electronic dispensing system reports are comparable to clinic cohort reports when used to identify individuals starting or continuing on antiretroviral therapy, but are easier to generate. In our setting, transmission of such reports to the central pharmacy would improve forecasting for the annual surge in ART dispensing, and reduce time when ART is not available. These reports could readily be used to identify those lost to care.

Chapter five: Population efavirenz pharmacokinetic data, cytochrome 2B6 genotyping and electronic adherence monitoring: successful prediction of virological response in a South African community-based ART-naïve cohort.

Authors:

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Synopsis:

This paper illustrated that while mid-dose efavirenz concentrations can predict treatment outcomes, metaboliser status does not; and that the current therapeutic lower limit of 1mg/ml may be too high.

Abstract.

Background: Efavirenz concentrations are highly variable, in part due to polymorphisms in cytochrome P450 (CYP) 2B6, which makes therapeutic drug monitoring (TDM) attractive. We hypothesised that efavirenz concentrations, with CYP 2B6 metaboliser genotype status, could predict virological outcomes.

Methods: South African ART-naïve participants were studied after initiation of efavirenz-based ART. CD4 cell count and HIV-RNA were determined at weeks 0, 16 and 48. Efavirenz mid-dose concentrations were drawn at weeks 16 and 48. CYP 2B6 genotyping (516G→T and 983T→C) determined metaboliser genotype status. Cox proportional hazards modelling was used to predict virological outcome. Comparison of Akaike Information Criterion values explored the most predictive lower limit of mid-dosing efavirenz concentration.

Results: 180 subjects with both efavirenz concentrations and HIV-RNA were studied. Median efavirenz concentrations were 2.3 mg/L (IQR1.6-4.6) and 2.21 mg/L (IQR1.5-3.9) at weeks 16 and 48 respectively. Extensive, intermediate or slow CYP2B6 metaboliser genotype occurred in 49 (27.2%), 84 (46.7%), and 39 (21.7%) participants respectively. Log₂ efavirenz concentrations [adjusted hazard ratio (aHR) 0.81, 95% confidence interval (95%CI) 0.72-0.92] and baseline CD4 cell count [aHR0.994, 95%CI0.989-0.998] were predictive of virological outcome. For each doubling in efavirenz concentration there was a 21% decreased hazard of virological failure; for each 50 cell increase in baseline CD4 count there was a 31% reduced hazard of non-suppression. The most predictive lower limit for mid-dosing efavirenz concentration was 0.7 mg/L.

Conclusion: Mid-dosing efavirenz concentrations predicted virological outcome. The currently recommended lower therapeutic limit (1 mg/L) for TDM is higher than our finding. CYP2B6 metaboliser genotype did not add predictive value.

Introduction.

Efavirenz is a good candidate for therapeutic drug monitoring (TDM) because there are reliable assays, its plasma concentrations are characterised by high inter-individual variability, low concentrations have been linked with viral non-suppression, and high concentrations with toxicity.(64, 65, 68) However, the relationship between efavirenz concentrations and viral suppression has not always been consistent in studies, perhaps due to the development of high level resistance to non-nucleoside reverse transcriptase inhibitors, which emerges rapidly with efavirenz-based ART. (64, 65, 68, 71, 164, 165)

The high inter-individual variability of efavirenz concentrations is explained in part by polymorphisms in *CYP2B6*, the gene which encodes for the cytochrome P450 (CYP) enzyme CYP2B6.(41, 166, 167) The prevalence of genetic slow metabolisers is high in sub-Saharan African populations.(41) Metaboliser genotype status (ultra-slow, slow, intermediate, or extensive) did not impact virological outcomes in a recent analysis of pooled studies conducted by the AIDS Clinical Trials Group, but the impact of genotype status on virological failure has not been fully explored in a South African population.(168)

The lower limit of the currently recommended therapeutic range (1-4 mg/L) for efavirenz is controversial. (165, 169, 170) Marzolini et al. reported that mid-dose efavirenz drug concentrations of less than 1 mg/L were associated with increased rates of virological failure.(169) While pharmacokinetic data from the 2NN study suggested an increase in virological failure with trough concentrations of <1.1mg/L, the authors did not recommend using this cut-off value to predict virological outcomes as the sensitivity was low.(170) Recently published data from the Encore 1 study noted that only a small proportion of those failing treatment had mid-dosing efavirenz concentrations of <1.0 mg/L. (165)

We hypothesised that mid-dosing interval efavirenz drug concentrations, together with knowledge of *CYP2B6* metaboliser genotype, would be predictive of virological outcome in a sub-Saharan African population starting first-line ART. We also examined the lower threshold concentration of efavirenz for therapeutic benefit.

Methods.

Participants, setting and standard of care:

Participants were recruited at the Hannan Crusaid Treatment Centre (HCTC), a large outpatient antiretroviral treatment centre in Cape Town. The cohort included ART-naïve adults and adolescents who were eligible if they had their own mobile phone and were willing to sign written informed consent.

All those entering the treatment programme at the HCTC received three group counsellor-driven treatment literacy sessions prior to commencing non-nucleoside reverse transcriptase inhibitor- (NNRTI-) based ART. (25, 33) They were also visited at home by a community care worker to confirm address and home circumstances. Those with a raised viral load or low adherence based on a count of tablet returns (<90%) received a stepped-up adherence package, including tailored counselling, monthly drug dispensing and further home-visits. Participants were traced by phone call and home visit if they were more than 4 weeks late for a clinic visit.

Sub-study design:

The parent study was a randomised controlled trial over 48 weeks investigating adherence to ART and has been described in detail elsewhere.(134) Participants also had the option of joining a non-randomised voluntary pharmacokinetic and pharmacogenetic sub-study, which required additional blood sampling.

Visits and sampling:

Sub-study visits included screening, baseline, weeks 16 and 48. Visits were timed to coincide with booked clinic visits to minimise inconvenience. Participants were reimbursed for local travel (R20 or ~US\$2) at each visit and offered a gift of a T-shirt, bag or mug valued at R80 (~US\$8) or less for each on-study visit.

Demographic and psychosocial details were collected at screening. Prescribed ART was recorded at baseline (week 0). Weight and current ART confirmed at all visits. Blood was drawn for CD4 cell count (FACS Count™, Beckton Dickinson, NJ, USA) and HIV-1 viral load (HIV-1 RNA 3.0 assay®, Bayer Healthcare, Leverkusen, Germany) at screen, and at weeks 16 and 48. At weeks 16 and 48, for those who gave additional consent, blood was drawn for in

a lithium Heparin tube for mid-dosing interval efavirenz concentrations, in the window between 9h and 16h after self-reported efavirenz intake time, and in an EDTA tube for *CYP2B6* pharmacogenetic analysis.

At weeks 16 and 48, most blood samples for efavirenz concentration and viral load were drawn on the same date. However, in a number of participants, viral load measurements were obtained up to 4 weeks before the scheduled pharmacokinetic visit (as part of standard of care) or afterwards (when the measurement had to be repeated due to issues with the measuring procedure). Samples were kept cold (4°C) until transfer to the laboratory within 2-3 hours of blood draw.

Pharmacokinetic analyses:

Samples were centrifuged at 3500 revolutions/minute for 10 minutes and plasma pipetted into cryovials which were labelled and frozen at -80°C. Samples were analysed for efavirenz concentrations using a validated liquid chromatography MS/MS method.

Pharmacogenetic analyses:

Samples were centrifuged at 3000 rpm for 30 minutes. The white blood cell layer (buffy coat) was transferred to a labelled cryovial and frozen at -80°C. Three *CYP2B6* single nucleotide polymorphisms (SNPs) previously associated with efavirenz concentrations were chosen and analysed: rs3745274 (516G→T), rs28399499 (983T→C) and rs4803419 (15582C→T). Genomic DNA was extracted from 100 µL of stored buffy coat, re-suspended in a total volume of 300 µL of lysis buffer and 30 µL of proteinase K from the Maxwell 16 LEV Blood DNA kit (Promega, UK) and incubated at 57°C for 30 minutes at 1000 rpm. The DNA was extracted as per manufacturer's instructions on the MaxWell automated extraction platform (Promega, UK) and eluted in 100 µL elution buffer.

The quantity and quality of extracted DNA was determined using the Qubit DNA BR Assay kit (Molecular Probes – Life Technologies, USA) and the Qubit 2.0 Fluorometer (Invitrogen – Life Technologies, USA) as per manufacturer's instructions. Once the quantity of DNA was determined it was diluted to 20 ng/µL using sterile nuclease-free water and 1 µL aliquoted into one well per sample in a 96 well plate. The DNA samples were left at room temperature for 12 hours, to lyophilize.

Amplification and genotyping of each participant for the presence of SNPs in their *CYP 2B6* gene was performed using fluorescently labeled minor groove binding (MGB) allele-specific probes (Applied Biosystems). Participants were genotyped for *CYP2B6* (516G→T, rs3745274; 983 T→C, rs28399499; and 15582 C→T, rs4803419), using 1 µL of lyophilized DNA and 1xTaqMan®Universal PCR Master Mix, No AmpErase® UNG (Applied Biosystems, Foster City, USA) to a total volume of 12.5 µL. The cycling conditions consisted of an initial enzyme activation step of 95°C for 10 minutes, followed by a denaturation step of 95°C for 15 seconds and a combined annealing and extension step for 1 minute at 60°C. All amplification reactions were performed on the ViiA7 (Applied Biosystems, Foster City, USA).

We used a simplified version of Holzinger et al's metaboliser status classifications, as used by Dooley et al.(166, 171) Each individual was classified as an ultra-slow, slow, intermediate or extensive metaboliser. The effect of 516GT|983TC SNP vector was tested as 4 metabolic subcategories: extensive metabolisers (EM) – 516GG|983TT, intermediate metabolisers (IM) - 516GT|983TT or 516GG|983TC, slow metabolisers (SM) – 516TT|983TT or 516GT|983TC, ultra-slow metabolisers (USM) – all participants 983CC irrelevant of 516 G→T genotype.(70, 166, 171)

Study outcome:

The outcome was viral load at week 16 or week 48.

Statistical analysis:

Descriptive statistics were used to summarise the baseline characteristics of the participant group and mid-dosing interval efavirenz concentrations using Stata 13.0 (Stata Corporation, College Station, USA)

Prediction of virological outcome: The change in the relative risk of viraemia was estimated using Cox proportional hazards regression model (Andersen-Gill repeated outcomes framework) with Efron approximation and interval censoring using the software R with package survival.(172-176) Each time interval runs from the preceding to the current viral load measurement. Viral loads were converted into dichotomised outcome: an event (classified as non-suppression) was defined as viraemia >400 copies/mL at week 16 and viraemia >40 copies/mL at week 48. The following variables were tested for their effect on

change in hazard of viral non-suppression: efavirenz concentrations, age, gender, baseline CD4, baseline viral load (\log_{10} -transformed) and metaboliser status.

Due to some pharmacokinetic and viral load (VL) samples falling before or after planned sampling window at week 16 and 48, time censoring was used. For samples scheduled for week 16 measurements taken between weeks 12 and 20 from treatment start were included in the analysis; for week 48 we analysed samples falling between weeks 32 and 64. Mid-dose efavirenz plasma concentrations were matched with viral load measurements taken on the same day or the next closest measurement within the time censoring interval.

Missing categorical covariates were imputed as the population mode and missing continuous covariates were imputed as population median. A sensitivity analysis was conducted to test the effect of these imputations by dropping all participants with imputed covariate values.

All variables were tested for their effect on the risk of viral non-suppression in a univariate analysis and included a priori in the full multivariate model. Backwards elimination process was performed starting with the covariate with the least significant p-value until all remaining predictors had $p < 0.05$ (final model).

Subsequently, the threshold of efavirenz mid-dosing concentration that was the most predictive of an increased risk of viral non-suppression (at levels described above) was derived as previously proposed by Bienczak *et al.* (177) Briefly, the threshold was selected by comparing the Akaike Information Criterion (AIC) values generated by Cox proportional hazard regression models testing efavirenz concentration dichotomised at different cut-off values. The AIC value was profiled by testing all models using concentration cut-offs between 0.1 and 5 mg/L in increments of 0.005 mg/L. The cut-off resulting in the lowest AIC value was chosen as the desired threshold, since this corresponds to the dichotomisation of efavirenz concentrations that is most predictive of virological non-suppression. The robustness of the estimated threshold was confirmed using a re-simulation approach: the original dataset was re-simulated 500 times introducing a normally distributed random error on the detected concentrations and the estimation procedure for the best cut-off value was repeated on each of the re-simulated datasets. The magnitude of the error was set to the unexplained residual variability estimated in population pharmacokinetic model by Dooley *et al.* (additive error = 0.0846 mg/L, proportional error = 9.31%. (171) The results of the re-

simulation procedure were used to derive 90% confidence interval on the concentration threshold (5th to 95th percentile of the values estimated from the 500 re-simulated data sets).

Ethical approval:

The University of Cape Town's Faculty of Health Science Research Ethics Committee gave approval to conduct this study. Each participant provided written informed consent. The trial was registered in the Pan African Clinical Trials Registry, number PACTR201311000641402.

Role of funding source:

The sponsors of the study had no role in the design and implementation of this study, nor in manuscript preparation. All authors had full access to the study data. CO developed the initial manuscript and all authors approved the submitted manuscript.

Results.

Baseline characteristics and genotypes:

One hundred and eighty of the 230 individuals enrolled into the parent study had matched efavirenz mid-dose concentrations and viral load data: 25 at week 16 only, 54 at week 48 only and 101 at both time points. Baseline characteristics are detailed in Table 5.1. The majority of this population were female. A total of 336 mid-dose efavirenz level samples were available from the 180 individuals: 170 at week 16 and 166 at week 48.

CYP2B6 genotype frequencies and metaboliser types are presented in Table 5.1. In this sub-Saharan African population, 20% of the cohort had slow or ultra-slow metaboliser status. The genotypes frequencies from all three SNPs were in Hardy-Weinberg equilibrium.

Table 5.1: Baseline characteristics of cohort used in the analyses.

Variable	Cohort with both efavirenz TDM and viral load		
	Baseline	Week 16	Week 48
Number: n	180	126	156
Female sex: n(%)	118 (65.6)	79 (62.6)	103 (66.0)
Age (years): median (IQR)	32.8 (27.4-40.7)	33.4 (28.1-41.4)	34.7 (28.8-42.6)
Weight (kg): median (IQR)	67.0 (58.4-79.8)	67.4 (59.1-79.1)	69.5 (59.0-80.0)
WHO stage: n(%)			
1	68 (37.8)		
2	36 (20.0)		
3	57 (31.7)		
4	19 (10.6)		
CD4 count (cells/mm ³): median (IQR)	229 (129-287)		
Log ₁₀ viral load (copies/mL): median (IQR)	4.9 (4.4-5.4)		
Viral load > 400 copies/mL (week 16) or 40 copies/mL (week 48): n(%)	180 (100)	8 (6.3)	18 (11.5)
Genotype CYP 2B6 516 G>T: n(%)			
GG	75 (41.7)	46 (36.5)	69 (44.2)
GT	73 (40.6)	56 (44.4)	64 (41.0)
TT	24 (13.3)	18 (14.3)	21 (13.5)
Missing:	8 (4.4)	6 (4.8)	2 (1.3)
Genotype CYP 2B6 983T>C: n(%)			
TT	131 (72.8)	94 (74.6)	117 (75.0)
TC	40 (22.2)	26 (20.6)	36 (23.1)

Variable	Cohort with both efavirenz TDM and viral load		
	Baseline	Week 16	Week 48
CC	1 (0.6)	0 (0.0)	1 (0.6)
Missing	8 (4.4)	6 (4.8)	2 (1.3)
Genotype CYP 2B6 15582C>T: n(%)			
CC	144 (80.0)	103 (81.7)	127 (81.4)
TC	27 (15.0)	17 (13.5)	26 (16.7)
TT	1 (0.6)	0 (0.0)	1 (0.6)
Missing	8 (4.4)	6 (4.8)	2 (1.3)
Metaboliser genotype: n(%)			
Extensive	49 (27.2)	31 (24.6)	44 (28.2)
Intermediate	84 (46.7)	60 (47.6)	77 (49.4)
Slow	38 (21.1)	29 (23.0)	32 (20.5)
Ultra-slow	1 (0.6)	0 (0.0)	1 (0.6)
Missing	8 (4.4)	6 (4.8)	2 (1.3)

Efavirenz concentrations:

Table 5.2 describes efavirenz concentrations by metaboliser genotype and visit week, using all efavirenz concentrations available. While the median (IQR) concentrations overall for each visit were within the recommended therapeutic range (1-4 mg/L), those with ultra-slow and slow efavirenz metaboliser genotype had higher median efavirenz concentrations throughout the study than those with extensive or intermediate metaboliser genotype (Table 5.2, Figure 5.1).

At weeks 16 and 48 a total of 10 (5.9%) and 13 (7.8%) participants respectively had efavirenz concentrations <1 mg/L, the majority of whom had extensive and intermediate metaboliser genotypes. At weeks 16 and 48 a total of 43 (25.3%) and 33 (19.9%) participants respectively had concentrations >4 mg/L, the majority of whom had slow or ultra-slow metaboliser genotype.

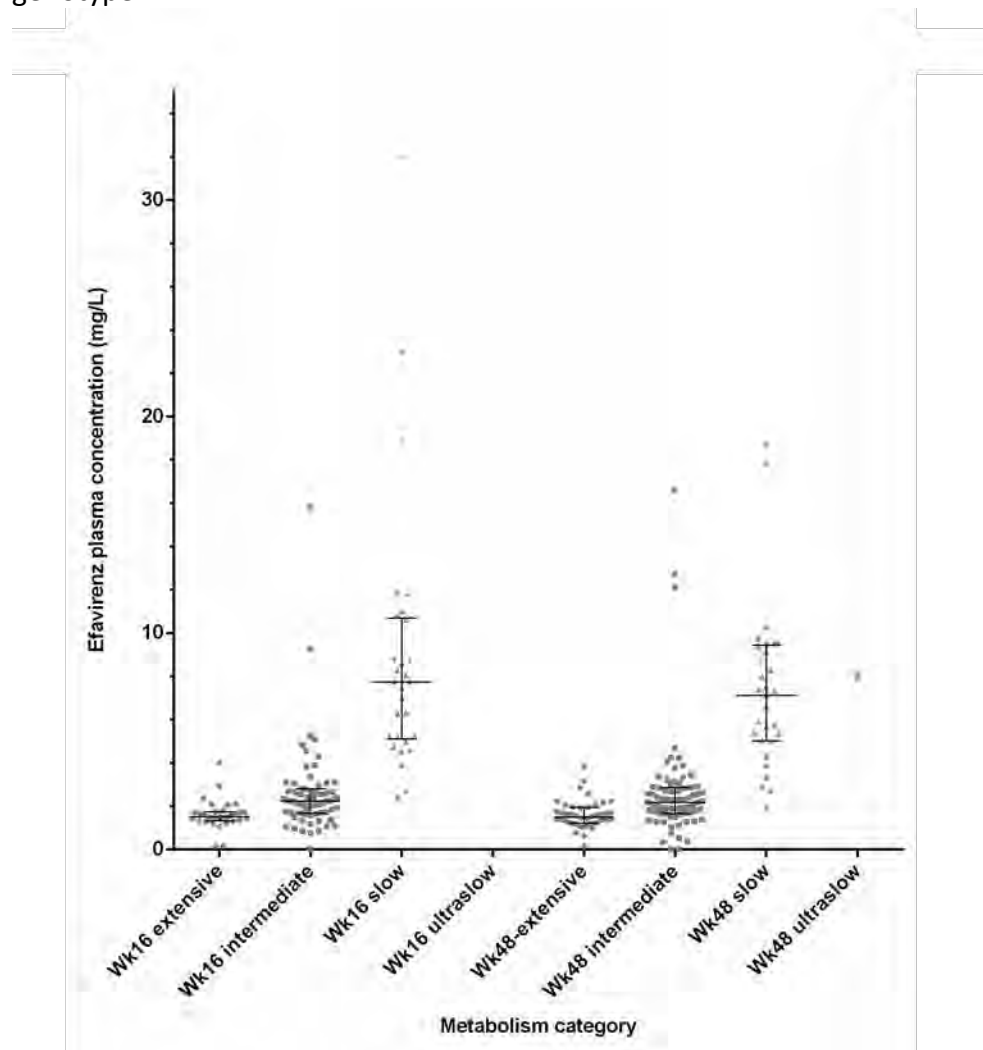
Table 5.2: Median (IQR) EFV concentrations in mg/L by visit week and metaboliser genotype.

Metaboliser genotype	EM	IM	SM	USM	p-value	Median	n
Week 16	1.51 (1.34-1.73)	2.24 (1.69-2.76)	7.75 (5.22-10.60)	-	<0.001	2.27 (1.64-4.60)	170

Week 48	1.50 (1.23-1.94)	2.19 (1.67-2.84)	6.79 (4.84-9.20)	7.98 (7.98-7.98)	<0.001	2.21 (1.53-3.91)	166
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EM –extensive, IM – intermediate, SM – slow, USM – ultraslow. p-value obtained through Kruskal-Wallis test.

Figure 5.1: Median (IQR) efavirenz concentrations in mg/L by visit week and metaboliser genotype.



Virological outcomes:

At 16 weeks 118 (93.6%) of 126 participants had a viral load of <400 copies/mL, 8 (6.4%) had viral loads >400 copies/mL. At 48 weeks 137 individuals (88.4%) of 155 participants had a viral load of ≤40 copies/mL; 27 (11.6%) had viral loads >40 copies/mL.

Virological outcome model:

Of the 180 participants, 101 contributed measurements at both time points, 25 only at week 16 and 54 only at week 48. We analysed a total of 281 matched viral load and plasma efavirenz mid-dose concentrations (126 at week 16 and 155 at week 48). The only categorical covariate with missing values was the metaboliser status, which was imputed in 10 patients as intermediate, the population mode. A sensitivity analysis was conducted by

dropping all participants with the missing values and revealed that the imputation had no significant effect on the results.

The results of univariate and multivariate analysis using the Cox proportional hazards model are presented in Table 5.3. Systemic exposure to efavirenz expressed as log₂ mid-dose concentration and baseline CD4 count proved to be the most significant predictors of the risk of viral non-suppression. The use of log-transformed efavirenz concentrations provided a better model fit than the use of the original values (results not shown) and it estimated a 23% decrease in the hazard of viral non-suppression (p=0.0005) for every doubling in drug concentration (corresponding to one unit increase in log₂ scale). Similarly, for every 50 cell increase in baseline CD4 count there was a 31.5% reduction in the hazard of non-suppression (p=0.0018).

Table 5.3: The results of Cox proportional hazards univariate and multivariate analysis.

Parameter	Univariate Models		Full Multivariate Model		Final Multivariate Model	
	HR (95% CI)	p-val	HR (95% CI)	p-val	HR (95% CI)	p-val
Log₂ efavirenz Conc [mg/L]	0.76 (0.64-0.91)	0.0035	0.78 (0.68-0.90)	0.0005	0.77 (0.67-0.89)	0.0005
Baseline log₁₀ VL	1.83 (0.94 - 3.53)	0.0734	1.40 (0.82-2.37)	0.2182		
Baseline CD4	0.9935 (0.9895- 0.9976)	0.0019	0.9945 (0.9908- 0.9983)	0.0040	0.9937 (0.9898- 0.9977)	0.0018
Age [years]	0.9639 (0.9111- 1.0200)	0.2010	0.9534 (0.8908- 1.0204)	0.1682		
Sex (ref. M)	0.5884 (0.2588- 1.3380)	0.2060	0.5289 (0.2090- 1.3388)	0.1789		
Metabolic Status (ref. FM + IM)	1.07 (0.43-2.65)	0.8810	1.78 (0.61-5.21)	0.2891		

HR – hazard ratio; CI – confidence interval; VL – viral load; FM – fast metaboliser; IM – intermediate metaboliser

There was a trend towards an increased risk of viremia for participants with a higher baseline viral load (for every 10 fold increase in the baseline viral load there was an 83% higher hazard of non-suppression $p=0.07$). No significant effect was detected for age, sex, and metaboliser genotype status.

All tested variables were included a priori in a “full” multivariate model, which found similar associations to the univariate analysis. After adjusting for the effect of other covariates, the trend towards increased risk of non-suppression for slow versus extensive combined with intermediate metabolisers increased, but still did not achieve statistical significance.

In the final multivariate model, higher efavirenz concentration and higher CD4 count were both associated with decreased risk of viral non-suppression. The analysis was repeated excluding participants with imputed covariate values, with no change to the associations observed.

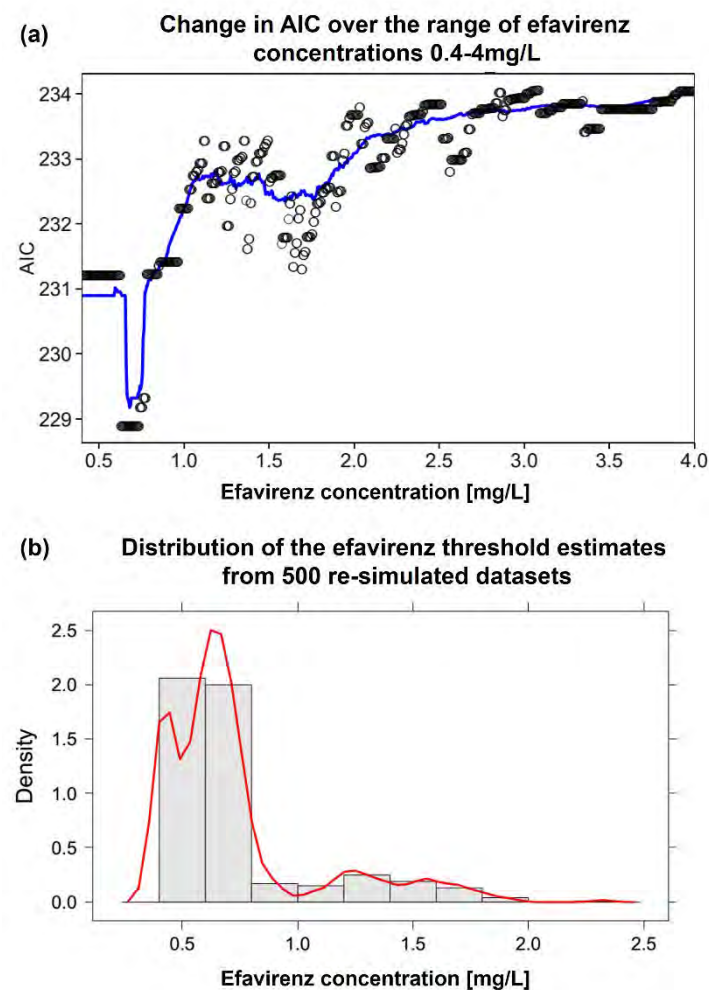
Threshold of mid-dose efavirenz concentration for prediction of non-suppression.

Dichotomised efavirenz concentration was then tested to identify the most predictive cut-off value. Figure 5.2a presents the profiling of the model AIC values when using efavirenz concentration cut-off values between 0.4 and 4 mg/L, while Figure 5.2b shows the distribution of the estimates obtained with the re-simulation procedure. The model with the lowest AIC value used a cut-off between 0.63 and 0.74 mg/L (90%CI 0.24-1.56), so the value of 0.7 mg/L was selected. Observations with efavirenz mid-dose concentrations below this threshold had 4.43 times greater hazard of virological failure (95%CI 1.58 -12.3, $p=0.004$).

The procedure was repeated using dichotomised concentrations in the multivariate model including the effect of baseline CD4 count, and it produced a similar value (results not shown).

Figure 5.2a: the comparison of the AIC values in models with dichotomised efavirenz mid-dose concentrations using cut-off values ranging between 0.4 and 4 mg/L in increments of 0.005 mg/L. The dots represent the AIC values for each tested concentration cut-offs generated from the original dataset, while the blue line is the median AIC value for tested concentration cut-offs from 500 re-simulated data sets.

Figure 5.2b: the distribution of optimal cut-off values obtained from the 500 re-simulated datasets.



Discussion.

We found that mid-dosing interval efavirenz concentrations significantly predicted virological outcomes. Our model showed that the most predictive cut-off value for viral suppression was approximately 0.7 mg/L, which is lower than the currently recommended lower limit of 1 mg/L. Lower baseline CD4 cell counts were also predictive of poor virological outcome. The proportion of individuals in this South African cohort with heterozygous or homozygous variants in *CYP2B6* was similar to others reported from this community. (69, 70, 171) The higher efavirenz concentrations we found with slower metaboliser genotypes

were similar to those from other groups. (165) However, *CYP2B6* metaboliser genotype alone did not predict virological outcomes.

When testing the effect of efavirenz mid-dose concentration without dichotomising, the model found a 24% decrease in risk of virological failure for every doubling of efavirenz concentration. The use of log-transformed concentrations suggests that relative changes in efavirenz plasma levels (a fold increase), as opposed to absolute changes (an increase of 1 mg/L), are more robust predictors of reduction in risk of non-suppression, as previously reported in Bienczak *et al.* (177).

Our analysis raises the question of whether the lower limit of the currently recommended therapeutic range (1 mg/L) is too high. (169, 170) The Encore 1 study has shown equivalent virological outcomes with a 400 mg dose of efavirenz compared to the standard 600 mg dose, despite significantly lower efavirenz exposure. (165) Only a small proportion of those with efavirenz concentrations <1 mg/L failed in this study. Our model shows that the most predictive cut-off value for virological outcome was 0.7 mg/L. Previous studies have shown that *CYP2B6* metaboliser genotypes, which have a marked impact on efavirenz concentration, are not associated with failure. (168) The likely explanation for the lack of correlation between *CYP2B6* metaboliser genotype and virologic outcomes in our study and in the pooled ACTG studies is that other factors, notably adherence, are more important determinants of efavirenz concentrations.

Participants with lower CD4 cell count at baseline had a significantly increased hazard of virological non-suppression. Participants with high baseline viraemia had poorer virological outcomes, but this did not reach statistical significance in our model. Our data support earlier commencement of ART.

Our study has several limitations. Time of efavirenz dose was not observed, although most patients reported taking their medications in the evening. The timing of viral loads was not under the control of the study staff and resulted in a large number of efavirenz samples being excluded from the analysis because they fell outside our time windows. As the focus of this study was on virological outcomes, we did not collect adverse event data and could not assess the impact of metaboliser genotype or high efavirenz concentration on toxicity.

The wide confidence interval for the mid-dose efavirenz concentration cut-off we found is due to the fact that only a limited number of patients had a viral load >400 c/mL at week 16 and/or 40 c/mL at week 48. A larger study is needed to confirm our findings and increase the robustness of the estimated values.

In summary, we have shown that, in an ART-naïve cohort, efavirenz mid-dosing interval concentrations at week 16 and 48 predict virological outcome. In addition, we confirm that knowledge of an individual's metaboliser genotype is not *per se* predictive of viral non-suppression. Our analysis suggests that the currently recommended lower limit of therapeutic range for efavirenz is too high. Efavirenz TDM using a revised cut-off of 0.7 mg/L may be of use in a routine clinical setting, to identify patients at risk of virological failure.

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Chapter six: Comparison of traditional vs. electronic adherence measures in an ART-naïve cohort in a resource-poor setting - which best predicts virological or resistance outcome at 48 weeks?

Authors:

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Publication status:

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Synopsis:

This paper shows how differing measures of adherence: electronic monitoring using Wisepill®, self-report, tablet returns, drug concentrations and iDART pharmacy refill data, compare within one cohort at predicting virological failure and antiretroviral drug resistance. It also illustrates how an existing locally developed pharmacy database (iDART) can be used to monitor adherence.

Abstract.

Background: Incomplete adherence to antiretroviral therapy results in virologic failure and resistance, but it is unclear which of the many available adherence measures best predicts these outcomes. We compared real-time electronic methods with patient-reported and objective adherence measures in an ART-naïve cohort in South Africa.

Methods: We recruited ART-naïve participants from a community ART clinic. We prospectively collected demographic and disease data, CD4 count and HIV-RNA at weeks 0, 16 and 48. HIV-RNA >500 copies/ml triggered a genotype. We quantified adherence using self-report (SR), clinic-based pill count (CPC), average adherence by pharmacy refill (PR-average), calculation of medication-free days (PR-gaps), efavirenz therapeutic drug monitoring (TDM) and an electronic adherence monitoring device (EAMD). We modelled associations between adherence measures and virologic and genotypic outcomes using logistic regression, and derived the area under the curve (AUC) from the receiver operator characteristic (ROC) analyses to assess performance of adherence measures in predicting outcomes.

Results: we enrolled 230 participants. Median (IQR) adherence by the various measures was: SR 100% (100-100), CPC 100% (95-107), PR-average 103% (95-105), PR-gaps 100% (95-100) and EAMD 86% (59-94) at week 48. Efavirenz concentrations were therapeutic (>1mg/ml) in 92%. At week 48, retention in care was 81% (186/230), and 83% (155/186) achieved HIV-RNA <40 copies/ml. EAMD, PR-average and PR-gaps best predicted virological outcome at week 48 with AUC ROC of 0.73 (95%CI 0.61-0.83), 0.73 (95%CI 0.61-0.85) and 0.72 (95%CI 0.59-0.84) respectively. EAMD, PR-gaps and PR-average were all highly predictive of the presence of resistance mutations at week 48, with AUC ROC of 0.92 (95%CI 0.87-0.97), 0.86 (0.67-1.0) and 0.83 (95%CI 0.65-1.0) respectively. SR, CPC and EFV concentrations were poorly predictive of virological or resistance outcomes.

Conclusion: Adherence data from EAMD and pharmacy refill measures predicted resistance and virological failure similarly. Pharmacy refill data is a pragmatic option for monitoring adherence in resource-limited settings where electronic monitoring is unavailable.

Introduction.

Consistent ART adherence is critical to realising the clinical and prevention benefits of ART.(5, 16, 178). Despite this, there is no gold standard identifying adherence levels and/or patterns that place individuals at risk for virologic failure and drug resistance in a clinical setting.(44, 49, 54)

A variety of ART adherence measures have been used in both observational and intervention studies. Self-report is the most frequently used method, but is imprecise and overestimates adherence, similar to clinic-based pill counts.(44, 47, 49, 54) Pharmacy refill data also overestimate adherence, but are more consistently associated with virological failure and mortality. (57-59) Electronic drug monitoring methods have been most closely associated with virologic failure, despite underestimating adherence due to storage and ingestion of medications outside of the device (pocket-doses). (44, 54, 63) Therapeutic drug concentration monitoring has been associated with virologic outcomes, though its precision relative to other adherence monitoring approaches is poorly understood. (5, 64, 65)

Few studies have directly compared or ranked the ability of multiple adherence monitoring methods including subjective, objective, electronic and drug concentrations in one cohort to predict virological failure (42, 61, 79) and data comparing of multiple adherence measures with drug resistance is lacking.(179)

Our study compared six adherence measures: self-report (SR), clinic-based pill count (CPC), pharmacy refills (PR-average), calculation of medication free days or gaps (PR-gaps), therapeutic drug monitoring (TDM), and real-time electronic drug monitoring. All adherence measures were collected in a prospective ART-naïve cohort starting first-line ART, in order to explore which measure best predicted virological or resistance outcome at 16 and 48 weeks into treatment.

Methods.

Participants and setting:

This study is a sub-study of a randomised controlled study recruited at the Hannan Crusaid Treatment Centre, a large outpatient antiretroviral treatment centre in Cape Town. This site and the randomised study have been described in detail elsewhere (38, 134) The cohort included ART-naïve adults and adolescents starting first-line ART, who were eligible if they had their own mobile phone and were willing to sign written informed consent. In addition, all patients had a baseline CD4 count below 350 cells/ul or a stage 3 or 4 AIDs-defining illness in keeping with the national HIV guidelines for starting ART.(146)

Study design:

The parent study was a randomised controlled trial over 48 weeks investigating the impact of mobile phone message reminders when missed doses were detected by a real-time EAMD on adherence to ART. All participants received the EAMD on study entry to record daily ART dosing times. Real-time EAMD was measured using Wisepill®, which is the size of a mobile phone and holds a week of medication in an internal and removable seven compartment pill box container. Participants were instructed on refilling and replacing the internal pill box container weekly. On opening, a signal was sent via the mobile-phone network to a secure central computer, thus recording tablet taking or treatment interruptions in real time. This device has been used in other resource-limited settings. (60, 62) The main study did not show a difference in cumulative adherence by study arm, as measured by the EAMD, and this sub-study includes data from participants without reference to study arm.

All participants starting ART received three group counsellor-driven treatment preparedness sessions prior to commencing ART. (25, 33) They were visited at home by a community care worker to confirm address and ascertain home circumstances. All participants commenced a non-nucleoside reverse transcriptase inhibitor (NNRTI)-based first-line ART regimen. Counts of pill returns were done at each scheduled clinic visit. Those with a raised HIV-RNA (>1000 copies/ml) or non-optimal clinic-based pill count adherence (<90%) received additional adherence support, which included tailored counselling, monthly drug dispensing and

follow-up home-visits. Participants were traced by phone and home visit if they were more than 4 weeks late in attending a scheduled clinic visit.

Study visits:

There were six study visits: screening, baseline, weeks 16, 32 and 48, and end of study. Visits were timed to coincide with scheduled clinic visits to minimise inconvenience to the participant. Participants were reimbursed for local travel (~US\$2) at each visit and for the three on-study visits (weeks 16, 32 and 48) were given a gift of a T-shirt, bag or mug valued at R80 (~US\$8) or less. If participants came to a standard of care clinic visit but did not attend the corresponding study visit, tablet return and virological data were extracted from their clinic folder.

Demographic and psychosocial details, including age, gender, weight, height as well as assessments for depression, anxiety and alcohol use, were collected at screen. The 14-question Hospital Anxiety and Depression Score (HADS) was used to assess anxiety and depression and the CAGE score used to assess alcoholism.(147, 148) Blood was drawn for CD4 cell count (FACS Count™, Beckton Dickinson, NJ, USA) and HIV-RNA (HIV-1 RNA 3.0 assay®, Bayer Healthcare, Leverkusen, Germany) at baseline, 16 week and 48 week visits. Mid-dose efavirenz concentrations were drawn at weeks 16 and 48. The time of blood draw, and the self-reported time of most recent ART dosing were recorded. Finally, weight was measured and current ART confirmed at all visits.

Adherence data:

For pill counts, average pharmacy refill data and self-recall, the data used was that typically available to clinic staff during a consultation with a patient.

Three-day self-recall (SR): At weeks 16 and 48, study staff asked each participant: “Did you swallow your pills yesterday / two days ago / three days ago?” Percent doses taken over three days was calculated from the participants’ responses. Study staff were not part of the clinical team. Data were only available if a participant attended the study visit.

Clinic-based pill count (CPC): Participants were instructed to bring any remaining tablets to each study visit. Returned tablets were counted by the clinic counsellors. CPC adherence

was calculated using the difference between the number of tablets dispensed and the number returned and dividing by the number of days between the date of dispensing and the current visit date (adjusted for the number of doses per day). At week 16 this would give an adherence over the previous one month period and at week 48 an adherence over the previous two month period. For the analyses, only the tablet count related to dosing efavirenz, nevirapine or, for those who switched to second-line, lopinavir/r dosing was used.

Pharmacy refill – average method (PR-average): An electronic dispensing system (iDART) was used at the site to record the date of ART dispensed and the quantity given to each participant. (140, 180) Obvious errors, such as date and dispensing duplications were removed. A cumulative PR-average measure was obtained by dividing the number of days of efavirenz, nevirapine or lopinavir tablets each patient received between study randomisation date and either week 16 or week 48, by the number of days they were in care over the same period.

Pharmacy refill – gaps method (PR-gaps): This measure uses pharmacy dispensing volumes and refill visit dates to determine the number of medication-free days in a dispensing period. The method allowed for patients to accumulate medication within the study period given that most received two additional days of supply each 30 days dispensed. The number of medication-free days are subtracted from the number of days in the period, and divided by the number of days in the period to give an adherence percentage. The method has been shown to predict virological suppression. (58)

Therapeutic Drug Measuring (TDM): At weeks 16 and 48 visits a sample was taken to quantify mid-dosing interval efavirenz concentrations. Mid-dosing interval samples were drawn in the morning, after dosing the previous evening. Self-reported time of the evening dose was recorded. Samples were kept cold (4°C) until transfer to the laboratory within 2-3 hours of blood draw. Samples were centrifuged at 3500 revolutions/minute for 10 minutes and plasma pipetted into cryovials which were labelled and frozen at -80°C. Efavirenz concentrations were analysed using a validated liquid chromatography MS/MS method.

EAMD data: The daily EAMD data for each participant, from date of randomisation to weeks 16 or 48, were downloaded from the Wisepill® server. Each device is contacted by the

server daily, called a “heartbeat”, to determine functionality and record battery voltage. An adherent day was defined as any recorded EAMD opening from 06h00am on that day to 05h59am the following day. Days with battery voltage <3660V or no heartbeat were censored. Cumulative adherence data for EAMD was calculated as the number of adherent days divided by the number of days in care.

Study outcome:

The primary outcome was virological failure defined as a single HIV RNA of >400 copies/ml at week 16 or >40 copies/ml at week 48. (181, 182)

The secondary outcome was development of HIV-1 drug resistance. Genotype resistance tests were done on all those with HIV RNA >500 copies/ml (the minimum HIV-RNA for amplification) at weeks 16 or 48. Nucleic acid was extracted with the NucliSens EasyMag automated extraction system (bioMérieux, Boxtel, The Netherlands). Genotyping was performed by a reverse transcriptase PCR followed by a nested PCR and dideoxynucleotide terminator sequencing of PR and RT using a homebrew assay that amplifies HIV-1 nucleotide positions 2250 to 4229 (HXB2 numbering), spanning the complete PR gene and RT codons 1 to 262 and using gene-specific sequencing primers. (183) Participants with one or more major resistance mutation as defined by the 2014 IAS update of drug resistance in HIV-1, causing resistance to ≥ 1 of the three drugs in their regimen were classified as resistant.(184).

Each participant had one of four possible study end points:

Completed study: participants in care at the clinic on the date of the end of study visit.

Transferred out: participants transferred to another clinic for care during the study period and the transfer out date recorded.

Death: Date of death as recorded in the medical record.

Loss to follow-up (LTFU): Participants were considered LTFU if they had not attended the clinic for more than 12 weeks and were not known to have transferred out or to have died. The date of LTFU was taken as the last date they attended the clinic.

Statistical analysis:

Data were analysed using Stata 13.0 (Stata Corporation, College Station, USA). Descriptive statistics (number, percentage, median and interquartile ranges) were used to summarise the baseline characteristics of the participant group and to tabulate the adherence data.

All available adherence data were used from each individual who had a HIV-RNA drawn within a 4 week window around week 16 (weeks 12 to 20) or a 16 week window around week 48 (weeks 32 to 64) in a per-protocol analysis from the time they entered care until the date of the respective viral load.

Univariate and multivariate logistic regression models were used to explore each adherence measure's relationship to virological failure and genotypic resistance at weeks 16 and 48. Both outcomes were binary, categorised as described above. The data for each adherence measure was continuous. Other variables included in the models (age, baseline CD4 cell count and baseline HIV-RNA) were specified prior to the analysis. Receiver Operator Characteristics (ROC) were generated to view the overall predictive power of the univariate and multivariate models. The area under the curve derived from the ROC, with 95% confidence intervals, was used to compare the prediction of virological failure or resistance by each adherence measure.

We also explored associations between EFV concentration and virological failure by categorizing EFV concentrations as: below limit of quantification (0.0195mg/ml), >0.0195 to <1.0 mg/L or ≥ 1.0 mg/L. We used the Fisher's exact test to compare proportions. The \log_{10} values of EFV mid-dose drug concentrations were included as a continuous variable in the univariate and multivariate models described above. \log_{10} values shift the distribution curve of the EFV concentration values toward normal for regression modelling.

Ethical approval:

The University of Cape Town Faculty of Health Science Research Ethics Committee gave approval to conduct this study. Each participant provided written informed consent. The trial was registered in the Pan African Clinical Trials Registry, number PACTR201311000641402.

Role of funding source:

The sponsors of the study had no role in the design and implementation of this study, nor in manuscript preparation. All authors had full access to the study data. CO developed the initial manuscript and all authors approved the submission.

Results.

Two-hundred-thirty antiretroviral naïve HIV-positive participants were recruited onto the study between July 2012 and March 2013. Baseline characteristics are described in Table 6.1. The cohort is typical of other African ART cohorts, with a predominance of women. The majority were clinically well. More than a third of the cohort had anxiety or depression scores (>8) that required further assessment and 15% were alcoholic on CAGE score (≥ 2). A minority had not disclosed their HIV-status to any other person.

Table 6.1: Baseline demographic, clinical treatment and psychosocial characteristics of all 230 study participants.

Variable	Full cohort	With VL at week 16	With VL at week 48
Number: n	230	160	180
Female sex: n(%)	150 (65.2)	108 (67.5)	121 (67.2)
Age in years: mean (sd)	34.5 (9.1)	34.8 (8.9)	35.0 (9.4)
Height (cm): mean (sd)	164.0 (8.6)	164.1 (8.2)	164.0 (8.1)
Weight (kg): median (IQR)	67.3 (57.8-79.6)	67.2 (58.0-80.0)	68.1 (58.7-80.4)
BMI: median (IQR)	24.3 (21.3-29.8)	24.2 (21.5-29.9)	24.6 (21.5-30.7)
WHO stage: n(%)			
1	84 (36.5)	58 (36.3)	73 (40.6)
2	47 (20.4)	34 (21.3)	39 (21.7)
3	75 (32.6)	54 (33.8)	51 (28.3)
4	24 (10.4)	14 (8.8)	17 (9.4)
CD4 count (cells/mm ³): median (IQR)	225 (133-287)	229 (132-288)	233 (144-287)
Log HIV-RNA (copies/ml): median (IQR)	4.9 (4.4-5.4)	4.9 (4.4-5.4)	4.8 (4.4-5.4)
NNRTI at start: n(%)			
Efavirenz	228 (99.1)	158 (98.8)	178 (98.9)
Nevirapine	2 (0.9)	2 (1.2)	2 (1.1)
NRTI at start*: n(%)			
Tenofovir	225 (97.8)	159 (99.4)	177 (98.3)
Zidovudine	4 (1.7)	1 (0.6)	3 (1.7)
Stavudine	1 (0.4)	-	-
HADS depression score of 8 or above (borderline or case)**: n(%)	74 (32.1)	55 (34.3)	58 (32.2)
HADS anxiety score of 8 or above (borderline or case)**: n(%)	89 (38.7)	64 (40.0)	70 (38.9)
Non-disclosure: n(%)	11 (4.7)	8 (5.0)	7 (3.9)
CAGE score ≥ 2 : n(%)	35 (15.2)	22 (13.8)	25 (13.9)

* all were taking 3TC or FTC as a second NRTI.

** 14-question Hospital Anxiety and Depression Score.

Antiretroviral therapy:

All participants except two initiated efavirenz-based ART; and the remaining two on nevirapine-based ART. Both non-nucleoside reverse transcriptase inhibitors (NNRTI) were given with two background nucleoside reverse transcriptase inhibitors. Tenofovir was used in 97.8% (Table 6.1).

Retention in care:

At the end of the study 186 participants remained in care (80.8%) at the study site and a further 16 (7.0%) had transferred to care elsewhere. Eight participants (3.5%) had died and 19 (8.3%) were lost to follow up. One participant withdrew consent. The median number of days in care was 385 (364-415 days).

Virological outcome:

At week 16, 160 participants had HIV-RNA drawn within the 12 to 20 week window and 149 (93.1%) were suppressed to ≤ 400 copies/ml (Table 1). At week 48, 180 had a HIV-RNA available, of whom 154 (85.6%) were suppressed to ≤ 40 copies/ml (Table 6.1).

Adherence measures:

Table 6.2 describes the median adherence by each measure at weeks 16 and 48, for all participants with a HIV-RNA drawn at that visit. Self-report and efavirenz concentrations were only available if study protocols were completed. Tablet returns and pharmacy refill data were available for all those who attended the clinic, whether or not they attended for study procedures. EAMD data were available for all study participants.

The subjective measure, SR, gave the highest adherence with the most individuals reporting 100% adherence (median 100%, IQR 100-100%). Clinic-based pill count and both pharmacy refill measures also gave a median adherence of 100% at week 16 and 48, but widened inter-quartile ranges highlighted some variations within the participants. Cumulative adherence by the EAMD showed the lowest median adherence at both visits: 93% (IQR 74-98%) at week 16 and 86% (IQR 59-94%) at week 48. Median efavirenz concentrations were

2.3 (IQR 1.6-4.4)mg/L at week 16, and 2.1 (IQR 1.5-3.4) mg/L at week 48, both largely within the currently recognised therapeutic range of 1.0-4.0 mg/L at both time points.

Table 6.2: Median adherence percentage with inter-quartile range at each study visit, by adherence measure. Self-report and EFV concentrations are measured on the date of the visit. Tablet counts cover the 30 days (week 16) or 60 days (week 48) before the visit. Pharmacy refill and EAMD adherence are cumulative data from baseline to latest time in care.

	n	Week 16	n	Week 48
Self-report (%): median (IQR)	140	100 (100-100)	169	100 (100-100)
Pill count (%): median (IQR)	160	100 (92-100)	178	100 (95-107)
Average pharmacy refill (%): median (IQR)*	158	104 (101-105)	178	103 (95-105)
Gaps pharmacy refill (%): median(IQR)*	158	100 (100-100)	178	100 (95-100)
EAMD adherence (%): median (IQR)*	160	93 (74-98)	180	86 (59-94)
EFV concentration (mg/L): median(IQR)	136	2.3 (1.6-4.4)	156	2.1 (1.5-3.4)
Viral suppression: n(%)	160	149 (93.1)	180	154 (85.6)

*cumulative per protocol measures.

Failure prediction models:

At week 48, adherence measured by EAMD, PR-average, PR-gaps and TR significantly predicted virological failure (>40 copies/ml) both in univariate and multivariate analyses. Odds ratios and adjusted odd ratios for these models are presented in Table 6.3: The odd ratio gives the reduction in the risk of failure or resistance for each 10% increase in adherence as quantified by the specified method. Neither log mid-dosing interval efavirenz concentrations included as a continuous variable nor self-reported adherence predicted failure. For all multivariate models, an increased CD4 cell count at baseline was associated with reduced odds of failure. Four full models (EAMD and PR-average at weeks 16 and 48) are presented in supplementary Table 6.4.

Table 6.3: Odds ratios (OR) or adjusted odds ratios (aOR) with 95% confidence intervals (CI) for failure or resistance given a 10% increase in the adherence variable (or a 1 log increase in EFV concentration) in each logistic regression model. Univariate models use only the adherence variable in the model with the outcome variable, multivariate models include the adherence variable and three baseline variables (CD4 cell count, log HIV-RNA and age) with the outcome variable. There are four outcome variables: the risk of virological failure to >40 copies/ml at week 48, the risk of virological failure to >400 copies/ml at week 16, the risk of resistance (presence of ≥ 1 IAS major mutation at genotyping) at weeks 16 and 48.

Adherence measure	Univariate model		Multivariate model	
	OR (95%CI)	p-value	aOR (95%CI)	p-value
Virological failure (>40 copies/ml) at week 48:				
EAMD*	0.87 (0.82-0.94)	<0.001	0.89 (0.82-0.95)	0.001
PR-average	0.78 (0.70-0.88)	<0.001	0.78 (0.69-0.87)	<0.001
PR-gaps	0.69 (0.56-0.82)	<0.001	0.68 (0.56-0.82)	<0.001
CPC	0.89 (0.82-0.96)	0.004	0.88 (0.80-0.96)	0.004
Log ₁₀ EFV	0.40 (0.16-1.03)	0.059	0.52 (0.19-1.37)	0.184
SR	0.98 (0.89-1.08)	0.698	0.98 (0.88-1.09)	0.720
Resistance (presence of ≥ 1 major mutation) at week 48:				
EAMD	0.74 (0.64-0.87)	<0.001	0.68 (0.53-0.88)	0.003
PR-average	0.77 (0.69-0.87)	<0.001	0.77 (0.66-0.89)	<0.001
PR-gaps	0.74 (0.65-0.85)	<0.001	0.77 (0.66-0.89)	0.001
CPC	0.85 (0.77-0.94)	0.002	0.82 (0.69-0.98)	0.031
Log ₁₀ EFV	0.14 (0.04-0.45)	0.001	0.14 (0.02-0.78)	0.025
SR	0.92 (0.83-1.02)	0.102	0.92 (0.78-1.08)	0.316
Virological failure (>400 copies/ml) at week 16:				
EAMD	0.93 (0.86-1.01)	0.085	0.96 (0.87-1.06)	0.459
PR-average	0.68 (0.55-0.83)	<0.001	0.66 (0.50-0.73)	0.004
PR-gaps	0.64 (0.51-0.82)	<0.001	0.64 (0.47-0.88)	0.006
CPC	0.89 (0.78-1.03)	0.133	0.94 (0.78-1.13)	0.491
Log ₁₀ EFV	0.17 (0.04-0.75)	0.020	0.20 (0.03-1.47)	0.115
SR	0.92 (0.83-1.03)	0.163	0.98 (0.83-1.01)	0.765
Resistance (presence of ≥ 1 major mutation) at week 16:				
EAMD	0.93 (0.85-1.01)	0.085	0.96 (0.86-1.07)	0.435
PR-average	0.85 (0.72-0.99)	0.036	0.87 (0.72-1.06)	0.171
PR-gaps	0.85 (0.71-1.01)	0.066	0.88 (0.69-1.11)	0.287
CPC	0.90 (0.80-1.01)	0.069	0.93 (0.82-1.06)	0.316
Log ₁₀ EFV	0.34 (0.08-1.81)	0.228	0.43 (0.07-2.66)	0.362
SR	0.93 (0.83-1.03)	0.147	0.97 (0.85-1.11)	0.647

*EAMD = electronic adherence monitoring device data; PR-average= average pharmacy refill data; PR-gaps= pharmacy refill gaps data; CPC=clinic-based pill count data; EFV = efavirenz mid-dosing interval data; SR= 3-day self-recall data.

Table 6.4: Full multivariate logistic regression models predicting virological outcomes at week 16 and 48 using EAMD and PR-average adherence measure.

6.4a. Full model predicting virologic outcomes at week 48, with EAMD as the adherence measure (n=179)

Week 48 failure	Odds Ratio	Std. Error	p-value	95% confidence intervals
Week 48 EAMD	0.97	0.01	0.001	0.95-0.99
Age (years)	0.97	0.03	0.221	0.92-1.02
Baseline CD4	0.99	0.00	0.070	0.99-1.00
Log baseline VL	1.06	0.53	0.901	0.40-2.82

6.4b. Full model predicting virologic outcomes at week 48, with PR-average as the adherence measure (n=177)

Week 48 failure	Odds Ratio	Std. Error	p-value	95% confidence intervals
Week 48 PR-average	0.94	0.12	<0.01	0.92-0.97
Age	0.97	0.03	0.366	0.92-1.03
Baseline CD4	0.99	0.00	0.013	0.99-1.00
Log baseline VL	0.77	0.42	0.635	0.27-2.23

6.4c. Full model predicting virologic outcomes at week 16, with EAMD as the adherence measure (n=159)

Week 16 failure	Odds Ratio	Std. Error	p-value	95% confidence intervals
Week 16 EAMD	0.99	0.01	0.459	0.97-1.01
Age	0.87	0.05	0.024	0.77-0.98
Baseline CD4	0.99	0.00	0.007	0.98-1.00
Log baseline VL	3.99	3.44	0.109	0.73-21.6

6.4d. Full model predicting virologic outcomes at week 16, with PR-average as the adherence measure (n=157)

Week 16 failure	Odds Ratio	Std. Error	p-value	95% confidence intervals
Week 16 PR-average	0.91	0.03	<0.01	0.85-0.97
Age	0.88	0.05	0.029	0.78-0.98
Baseline CD4	0.99	0.00	0.014	0.98-1.00
Log baseline VL	9.07	10.8	0.063	0.89-92.5

The ROC curves in Figure 6.1a show the predictive value of each adherence variable on virological failure (univariate models) at weeks 48. Figure 6.2 is a comparison of AUC ROC for each measure, with 95% confidence intervals. EAMD (ROC AUC 0.73, 95%CI 0.61-0.83),

PR-average (ROC AUC 0.73, 95%CI 0.61-0.85), and PR-gaps (ROC AUC 0.72, 95%CI 0.59-0.84) best predicted failure.

At week 16, using <400 copies/ml as the definition of failure, analyses showed that both pharmacy measures were predictive of failure, in both univariate and multivariate models. Log₁₀ EFV concentration also reached significance in the univariate model (for every 10 times or 1 log increase in EFV concentration, the odds of failure reduced by 83%), but the other adherence measures did not (Table 6.3 and Figure 6.3b).

Figure 6.1: Receiver Operating Characteristic (ROC) curves showing prediction of virological failure (>40 copies/ml) and resistance at week 48 by six adherence measures. Univariate model data are shown.

Figure 6.1a shows prediction of virological failure to <40 copies/ml at week 48 using adherence measures at week 48.

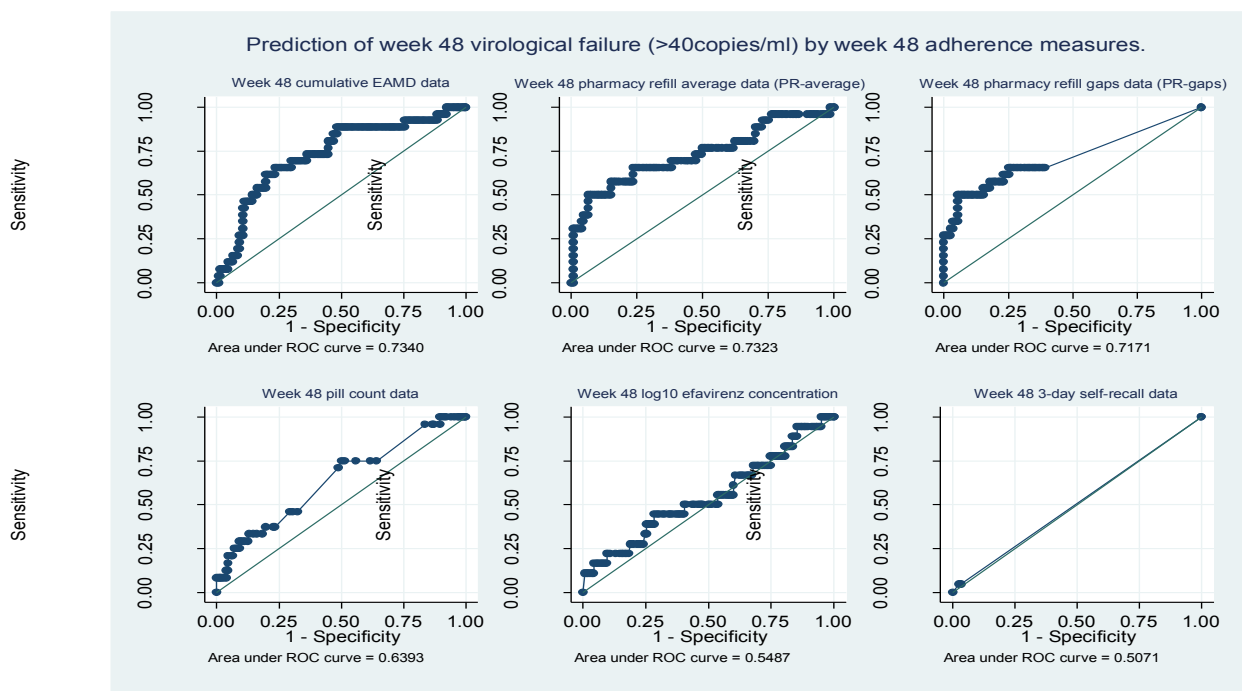


Figure 6.1b shows prediction of resistance at week 48 using adherence measures at week 48.

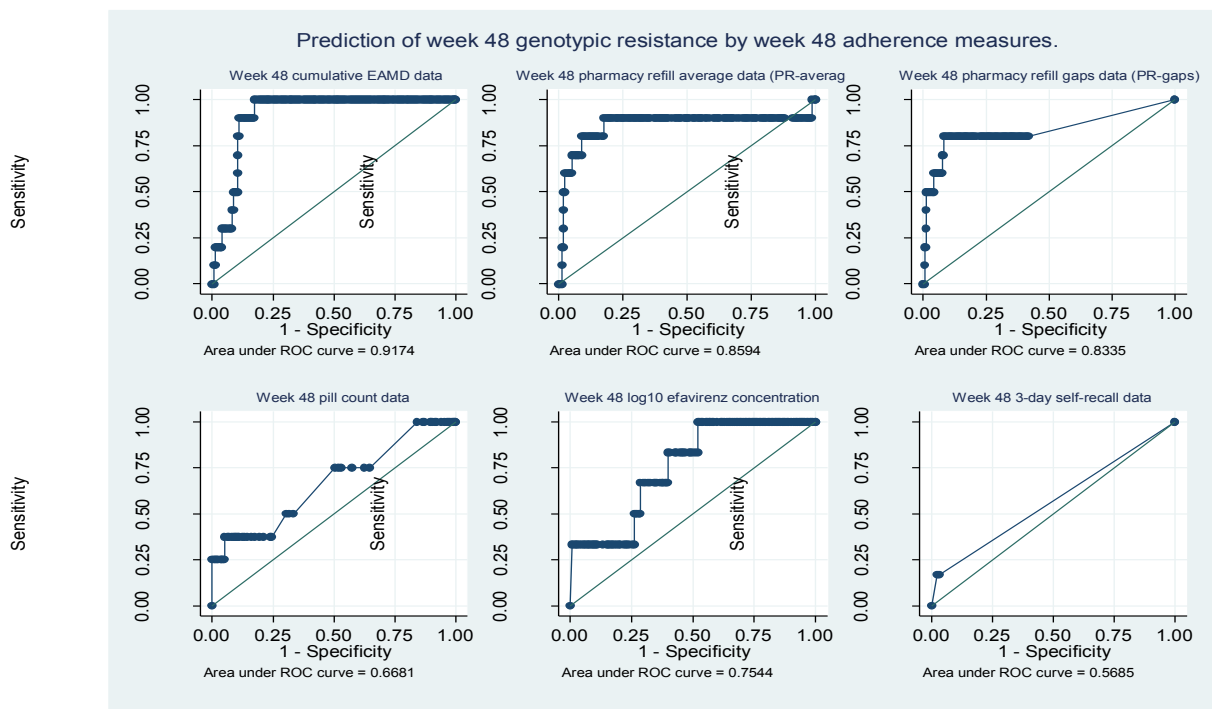
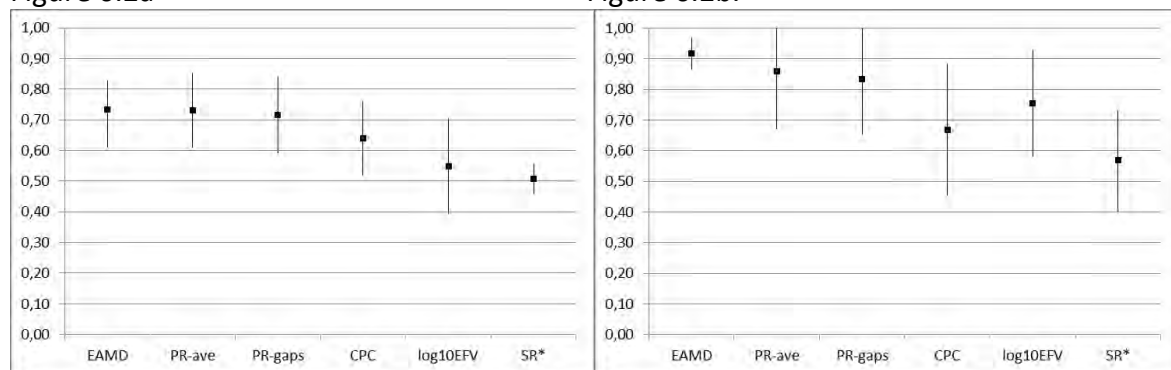


Figure 6.2: Comparison of AUC ROC, with 95% confidence intervals, for week 48 virological failure (Figure 2a) and week 48 resistance (Figure 2b), by each of six adherence measures.



*EAMD: electronic adherence monitoring device data; PR-ave: pharmacy refill average data; PR-gaps: pharmacy refill gaps data; CPC: clinic-based pill count data; EFV: spot efavirenz concentrations; SR: 3-day self-recall data.

Categorical analysis of EFV concentrations:

At week 48, using the Fisher Exact test, those with an EFV concentration below the limit of quantification ($n=3$) were more likely to fail ($p=0.046$) than those with sub-therapeutic concentrations (>0.0195 to <1 mmol/L, $n=9$) or those whose concentrations were therapeutic (≥ 1.0 mmol/L, $n=144$). At week 16 there was no relationship between the same three categories of EFV concentration and virological failure.

Resistance outcome:

All 14 of the participants whose HIV RNA was >400 copies/ml at week 16 qualified for HIV-1 resistance genotyping. One specimen was lost and one could not be amplified (HIV-RNA 534 copies/ml). Two of the remaining 12 participants had no major resistance mutations. Eight (66.7%) participants expressed the K65R mutation, conferring resistance to tenofovir, and three the M184V mutation, conferring resistance to lamivudine/emtricitabine. Of those with K65R at week 16, four continued to have raised viral loads at week 48, one transferred to care elsewhere, so week 48 data was not available, and three had suppressed virus. Two of the four with raised viral loads continued to have the K65R mutation present at week 48, and two did not. Of the three patients with the M184V mutation at week 16, all had raised viral loads at week 48. The M184V mutation was seen in two of these.

All 10 who expressed resistance had NNRTI mutations, including L100I, K101E, K103N, V106M, Y181C, Y188C/Y/L, G190A/G/S and H221HY. Despite only efavirenz and nevirapine being used, mutations conferring resistance to etravirine and rilpivirine were noted in 3 participants: one each of V90I, E138A and V179D. Supplemental Table 6.5a shows the resistance patterns expected from these mutations. The majority of those failing with available genotype had high level resistance to the NNRTI and tenofovir by week 16.

Twenty-seven participants had a HIV RNA of >40 copies/ml at week 48. Fourteen (51.9%) had HIV RNA >500 copies/ml and qualified for HIV-1 resistance genotyping. One specimen was lost and two could not be amplified (HIV-RNA 2331 and 45745 copies/ml). One of the remaining 11 participants had no major resistance mutations. Two (18%) participants expressed the K65R mutation and four (36%) the M184V mutation. As at week 16, the majority of the remaining mutations, in all 11 who expressed resistance, were NNRTI mutations, including L100I, K101E, K103N, V106M, Y181C, G190A, H221HY and F227L. Again, mutations to etravirine and rilpivirine were noted in 3 participants: one with E138A and two with V179D. Supplemental Table 6.5b shows the expected resistance patterns. The majority of those failing with available genotype had high level resistance to the NNRTIs.

Tables 6.5a and 6.5b. Resistance patterns for those with raised HIV-RNA that could be amplified at weeks 16 and 48: n(%), according to the Stanford University HIV Resistance Database genotypic interpretation algorithm.

Table 6.5a: resistance patterns at week 16.

Week 16	Susceptible	Low level resistance	Intermediate resistance	High level resistance	n
Lamivudine (3TC) or emtricitabine (FTC)	2 (16.7)		7 (58.3)	3 (25.0)	12
Abacavir (ABC)	2 (16.7)	1 (8.3)	7 (58.3)	2 (16.7)	12
Zidovudine (AZT)	11 (91.7)	1 (8.3)			12
Stavudine (d4T)	3 (25.0)	1 (8.3)	8 (66.7)		12
Tenofovir (TDF)	4 (33.3)			8 (66.7)	12
Efavirenz (EFV)	2 (16.7)			10 (83.3)	12
Nevirapine (NVP)	2 (16.7)			10 (83.3)	12
Etravirine (ETR)	4 (33.3)	2 (16.7)	5 (41.7)	1 (8.3)	12
Rilpivirine (RPV)	4 (33.3)	1 (8.3)	2 (16.7)	5 (41.7)	12

Table 6.5b: resistance patterns at week 48.

Week 48	Susceptible	Low level resistance	Intermediate resistance	High level resistance	n
Lamivudine (3TC) or emtricitabine (FTC)	6 (54.5)		1 (9.1)	4 (36.4)	11
Abacavir (ABC)	6 (54.5)	2 (18.2)	1 (9.1)	2 (18.2)	11
Zidovudine (AZT)	11 (100)				11
Stavudine (d4T)	7 (63.6)		3 (27.3)	1 (9.1)	11
Tenofovir (TDF)	8 (72.7)	1 (9.1)		2 (18.2)	11
Efavirenz (EFV)	1 (9.1)			10 (90.9)	11
Nevirapine (NVP)	1 (9.1)			10 (90.9)	11
Etravirine (ETR)	5 (45.5)	1 (9.1)	3 (27.3)		11
Rilpivirine (RPV)	5 (45.5)	2 (18.2)	1 (9.1)	2 (18.2)	11

Resistance prediction models:

Each adherence variable was modelled against the risk of resistance alone (univariate) and with age, CD4 cell count at baseline and log baseline HIV-RNA (multivariate) in logistic regression models for prediction. Adherence as quantified by EAMD, PR-average, PR-gaps, TR and log₁₀ EFV concentration were all significantly predictive of resistance in both univariate and multivariate analyses at week 48 (Table 3). Self-report was non-significant in either model. Reduced age and decreased CD4 cell count at baseline significantly increased the odds of resistance in all multivariate models at week 48.

The area under each of the receiver operator characteristic curves in Figure 6.1b shows the predictive value of each adherence measure in the univariate models on resistance at weeks 48, with 95% confidence intervals for inter-measure comparison shown in Figure 6.2b. While cumulative EAMD best predicted resistance with the narrowest 95% confidence intervals (AUC ROC 0.92, 95%CI 0.87-0.97), it was not significantly better than either pharmacy refill measure (PR-average AUC ROC 0.86, 95%CI 0.67-1.0; PR-gaps AUC ROC 0.83, 95%CI 0.65-1.00).

Only PR-average predicted resistance at week 16 (AUC ROC 0.72, 95%CI 0.57-0.90). ROC data from the univariate models is presented in Figure 6.3b and odds ratios in Table 6.3. Reduced age and decreased CD4 cell count at baseline significantly increased the odds of resistance in all multivariate models at week 16.

Figure 6.3 Receiver Operating Characteristic (ROC) curves showing prediction of failure (>400 copies/ml) and resistance at week 16 by each of the six adherence measures: figure 6.3a shows the AUC ROC using >400 copies/ml as the definition of failure; and figure 6.3b shows the prediction of genotypic resistance at week 16 by each of the six adherence measures.

Figure 6.3a shows prediction of virological failure to <400 copies/ml at week 16 using adherence measures at week 16.

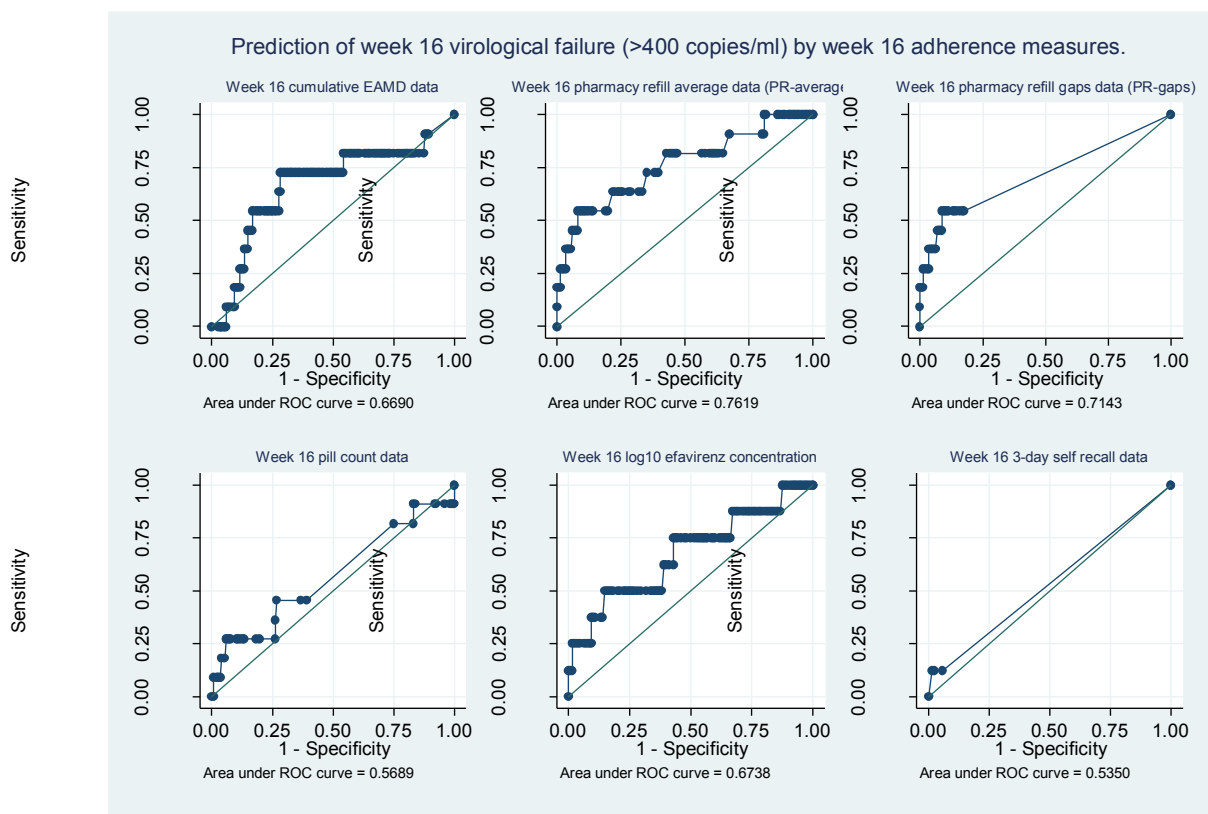
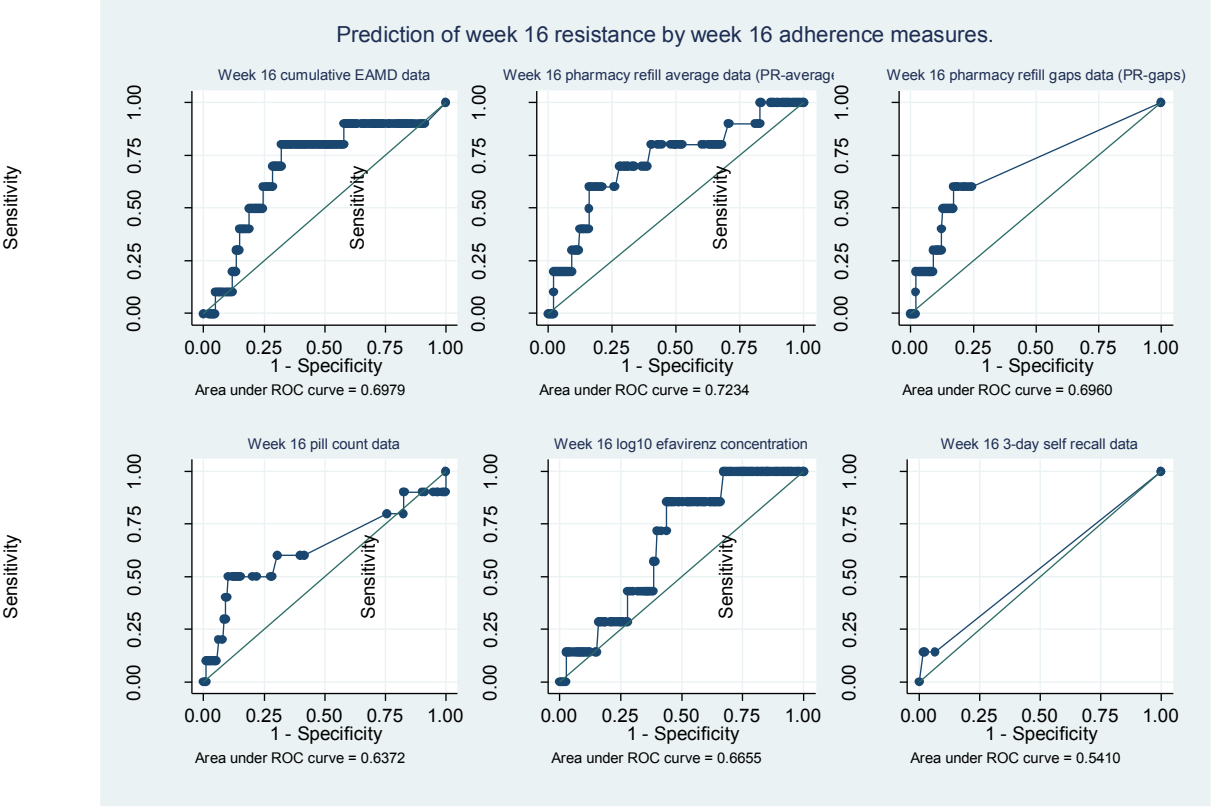


Figure 6.3b: Prediction of week 16 genotypic resistance by week 16 adherence measures.



Discussion.

We found high levels of adherence using both spot and cumulative measures. SR yielded the highest adherence estimate, but was not significantly associated with viral suppression or resistance outcomes. We found that cumulative EAMD adherence data and pharmacy refill measures best predicted virological failure and development of resistance at week 48.

Pharmacy refill measures best predicted failure and resistance at week 16.

Self-reported adherence measures to monitor adherence are widely used. (50-53) Most studies find that self-reported measures overestimate adherence, likely due to recall and social desirability bias, making this measure unreliable for research purposes or clinical monitoring. However, a self-report of incomplete adherence can be clinically useful in triggering adherence intervention. (55)

In contrast, four of the five objective adherence measures predicted virological failure: CPC, PR-average, PR-gaps and EAMD data. Average pharmacy refill data has been shown to predict virological outcomes and mortality reliably in the past. (5, 57, 59) Our group has shown that short term pharmacy gap adherence predicted virological failure on second-line ART. (58) Software to calculate PR-average or PR-gaps could easily be added to electronic dispensing systems, which are widely used in resource-limited settings. Clinic-based pill count is not widely recommended as it are subject to “pill dumping” and can be complex to perform in a large clinic. (5) Nonetheless, CPC performed reasonably well in this study.

While EAMD are often considered the gold standard adherence measure they not routinely used in clinical care. However, recent data shows EAMD can reduce costs associated with HIV RNA monitoring and real-time devices can detect early virologic rebound before established failure. (5, 185, 186) With the availability of newer, more affordable real-time technologies, electronic strategies should be reconsidered.

In categorical analysis, at week 48, the three participants with EFV concentrations below the limit of quantification were more likely to have virologic failure. By altering the distribution of the concentrations through the use of log values in the regression model, we found that the log values of mid-dose EFV concentration were predictive of resistance at week 48, with wide confidence intervals, but not of failure. Most drug concentrations were therapeutic, possibly reflecting white coat pre-visit dosing, leaving few with concentrations below therapeutic where virological failure would be more likely. The few participants with sub-

therapeutic concentrations limit the interpretation of this data. Larger studies including more participants with sub-therapeutic EFV concentrations are needed to adequately explore the ability of TDM to predict virological failure and resistance.

Most of those remaining in care at both week 16 and week 48 had virological suppression. However, the majority of those who had detectable HIV RNA also had resistance that would compromise at least one drug in their antiretroviral regimen, even at 16 weeks into therapy. While both pharmacy refill adherence measures at week 16 predicted virological failure to < 400 copies, only the PR-average method predicted this early resistance. Using early pharmacy refill data to predict those with failure is practical and easy to achieve. EAMD data was highly predictive of resistance at week 48, as were both pharmacy refill measures and, to a lesser extent, pill count data.

The collection of multiple adherence measures, prospectively in a single cohort is a strength of our study as it allowed direct comparison of multiple adherence measures, which has not been achieved in many other studies.(61, 64) Our study was based on maximum use of existing adherence data and used a per protocol approach to analysis, with those who did not have virological data at weeks 16 or 48 treated as missing for the predictive models. Losses to care in this cohort were similar to those previously reported at this site, and all participants had data included in the cumulative adherence measures. (40, 154) A study limitation, however, was that SR and CPC data were only available for the one or two months preceding the week 16 or 48 visit and not over the complete study period. These measures may have performed better over a cumulative period.

In conclusion, adherence as measured by pharmacy refill measures and electronic monitoring were the best predictors of resistance and virological failure in this prospective study. Pharmacy refill data is widely available and would be the more immediately implementable option, particularly in resource-poor settings, but consideration should be given to the use of either measure as preferable adherence monitoring strategies.

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Chapter seven: Discussion and conclusion.

7.1. Synthesis of results.

Objective one: The primary outcome of the randomised controlled trial (Chapter three) answered the first objective of this thesis. Text reminders after missing a dose did not improve cumulative adherence nor improve retention in care. However, text reminders did alter adherence behaviour, but these changes were more subtle than we anticipated. Messaging reduced the number of treatment interruptions of more than 72 hours and altering adherence patterns. Such detail of daily adherence patterning can only be explored using electronic adherence monitoring; all other measures give less granular data e.g. median adherence over the past month. (187) The impact of the text messages could also be seen in the tendency of those in the intervention arm to wait for the message before dosing (Figure 3.2).

Objective two: The iDART system can be used to monitor adherence and retention in care more accurately. Two adherence measures generated from pharmacy dispensing data were shown in Chapter six to be equivalent in predicting virological failure and resistance at week 48 to the Wisepill device. In addition, Chapter four showed that the pharmacy database more rapidly and accurately identified those who discontinued care than standard cohort reporting processes. Generating lost to care or discontinuation reports for tracing also took less staff time with iDART than cohort reporting. This is important as ART access expands and resources in sub-Saharan Africa become further stretched. Adherence in many local cohorts continues to be monitored using tablet return and self-report, while pharmacy data is available but neglected.

Objective three: In an ART-naïve population efavirenz levels might be expected to be predictive of virological outcomes. This was not evident using multivariate linear regression modelling (Chapter six) at week 16 or 48, due to small numbers of individuals with sub-therapeutic efavirenz concentration at either time point.(65, 68) Efavirenz is routinely overdosed, using the 600mg dose, with many more people having supra-therapeutic levels (>4mg/L) than sub-therapeutic levels (<1mg/L).(165) Log transformation of the efavirenz concentrations allowed for better exploration of the lower range of efavirenz concentrations (Chapter five). Both log efavirenz concentrations and baseline CD4 count

were predictive of virological outcome using Cox proportional hazard modeling that included all available efavirenz concentration data.

Whereas slower metaboliser status was linked to increased EFV concentration, it was not linked to virological outcome. Slowing of cytochrome 2B6 metabolism from wild type tends to increase efavirenz levels to above the therapeutic range. (71, 164, 168) Analysis also showed a cut-off mid-dose efavirenz concentration of 0.7 mg/L as the most predictive lower limit related to a decreased risk of virological failure. This contributes to growing data suggesting the lower limit of the normal therapeutic range (1.0mg/L) is too high (1mg/L).(165)

Objective four: Comparison of multiple adherence measures was presented in Chapter six. While adherence in the RCT cohort was generally good (Table 6.2), reflective of the whole Gugulethu cohort, two measures stood out.(38) Cumulative Wisepill electronic adherence data and pharmacy refill data were significant predictors of both virological failure and development of HIV-1 resistance. Use of these measures would reduce the discrepancy between adherence and virological outcome seen with the use of pill count data.(38) Data from Wisepill is more granular and can be responded to on a daily basis, but pharmacy refill measures are widely available. Tablet returns and efavirenz concentrations were less good at predicting virological failure, while self-report obtained from routine questioning had no value.

7.2. Discussion.

Impact of electronic reminders

Adherence:

On review of the literature pertaining to electronic reminders in ART, it appeared that reminder text messages after a missed dose should benefit adherence. While the ideal format of messaging intervention was not completely clear (page 82), in 2012, success had been shown with weekly messaging, which did not induce message fatigue.(50, 107)

Assuming a median adherence of 90%, based on prior data from this cohort, we anticipated that missed dose reminder messages would need to be sent once a week or less.(38) Simple message content to act as a dose trigger also appeared adequate, as studies using motivational messages did not show added benefit related to the messaging type.(107)

Sabin et al designed a study in China that was very similar to ours, with reminders sent 30 minutes after a missed dose, also based on the adherence literature as of 2012.(62)

However, in contrast to our study, her intervention showed strong adherence benefit. Our intervention did not show benefit on cumulative adherence, nor on virological outcome.

One important aspect where our study differed from that of Sabin et al, is that we studied only ART-naïve patients. Our cohort of ART-naïve adults showed relatively good median adherence (over 80% using Wisepill and 90% with other measures), with more than 67% (155/230) of those starting ART achieving viral suppression at a year at the site. All patients in this cohort received pre-treatment education and adherence support from a counselor if pill count adherence was less than 90%, or their week 16 viral load was raised. It is likely that the effect of the adherence intervention was minimised by the many who were adherent, and who would have been adherent even without any intervention. We were looking for an effect where the signal, poor adherence, was small. All of the studies reviewed which pre-selected known non-adherent patients showed adherence and/or biological benefit (Figure 2.8). (51, 53, 62) The results were more diverse when naïve participants were included. (50, 107, 130, 131, 135)

The Wisepill reminder text message intervention was largely designed to impact on daily medication dosing. We assumed that most missed doses were forgotten or missed accidentally. If this was this case, then a dosing reminder should be enough to initiate a dosing process. A non-response to a reminder implies more purpose than forgetfulness to the missed dose. While a large proportion of missed doses have been attributed to forgetfulness, other reasons for missing doses must also be considered.(142, 188)

The median age in our population was 34.5 years. For every 10 years younger there was a 27% reduction in the odds of pills being taken. Younger people are already known to be at risk of poor adherence.(189) Despite the expectation that younger people would respond positively to the use of mobile phone technology, we did not see this in our study, and there are there no other studies in the literature examining whether mobile phone technology can be used specifically to reach the young.

Non-disclosure is a commonly cited reason for poor adherence , but in our study only a small proportion of individuals (<5%) had not disclosed their HIV status to any others. However, depression, anxiety and alcohol use, which might lead to more missing of doses, were highly prevalent (Table 3.1). Management options for these mental illnesses in the South African public sector are limited. Social isolation or issues of stigma were also not addressed in this study. Others have attempted to address social isolation with text messaging: for example, Pop-Eleches designed motivational text messages with the assistance of the local staff and community, but no benefit over simple reminders was shown.(107, 133, 135) Mental illness and social isolation might be better addressed by direct human contact. Bidirectional messaging, generating a phone call as a response to a request or on non-response to a text requiring a reply, does seem to improve adherence and potential biological outcomes: two of the three studies with biological benefit allowed for a phone call to those in need.(50, 53)

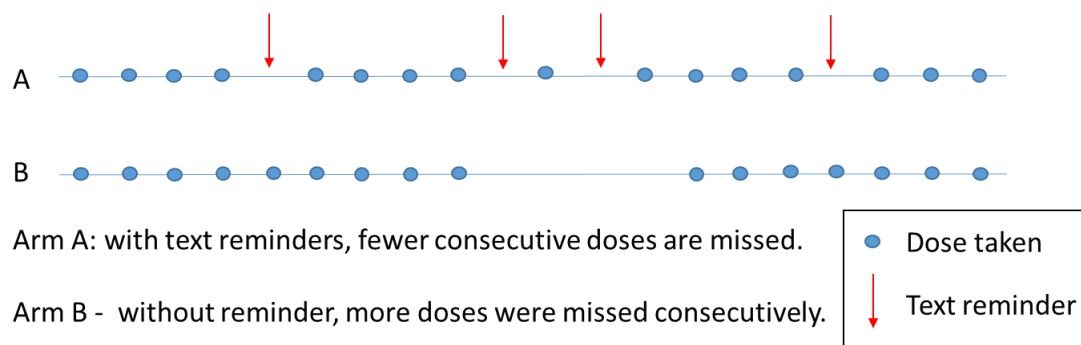
While there remains some need for human interaction, as well as electronic reminders, this support does not need to be provided by expensive clinicians. Task-shifting to nursing staff is already common practice in South Africa.(81, 116) Less-intensive models of care supported by lay staff and encouraging patients to form their own networks of support have shown great success (page 56).(13, 115) Perhaps a further step to community-based care could be taken for stable patients.(101)

Treatment interruptions:

The reduction in treatment interruptions of >72 hours in the intervention arm of the RCT has important implications. Treatment interruptions increase the risk of resistance and it is important to minimise them.(17, 38, 43) Regular messaging prompted individuals to dose at least once every three days, compared to the control arm where there were longer gaps in treatment (Figure 7.1).

Figure 7.1:

80% adherence: schematic showing different patterns when 16 of 20 doses were taken.



The pharmacokinetic profiles of tenofovir and efavirenz with longer half-lives, may maintain therapeutic drug concentrations with dosing every third day.(17) Real-time electronic adherence monitoring could allow exploration of a range of interventions to address treatment interruptions immediately as they happen, in order to prevent both viral rebound, with potential resistance development, and treatment discontinuation.

Some populations were at increased risk of treatment interruptions, including younger people (Chapter 3), where the relative count of treatment interruptions increased by 14% for every 10 year decrease in age. Men, and those with high depression scores, were also at increased risk of treatment interruption and might benefit from electronic reminders or another real-time intervention.

Retention in care:

While the focus of the study was the impact of electronic reminders on adherence to daily dosing, or adherence ‘implementation’, we also examined retention in care at 48 weeks. The outcomes of participants included in the RCT were entirely reflective of the cohort in care at the site at a year. This included rates of transfer to other sites, deaths and rates of treatment discontinuation.(40)

In the RCT cohort, 19 individuals (8.2%) were lost to follow up by a year, which matches cohort data from the same cohort in 2010 and 2013, and was less than the anticipated 10% when designing the RCT.(140, 154) Of note, most (more that 50%) of these losses to care occurred before week 16, and all before week 32 i.e. very early on in treatment.(190)

A further 16 individuals (6.9%) were transferred to care at other clinics during the year.(40, 154) Those who were lost to follow-up or who transferred out were again more likely to be young. The text message intervention also did not have any impact on loss to follow-up, or on transfers to care elsewhere.

In summary, while the text message reminders did not improve overall adherence or viral suppression, some interesting lessons were learnt. The impact of reminders on treatment interruption is significant and requires more exploration; younger adults were at higher risk of poor adherence, loss to care and treatment interruptions; and the impact of the text messaging reminders might have been maximized by identifying non-adherent individuals prior to intervening.

Adherence measurement methodologies

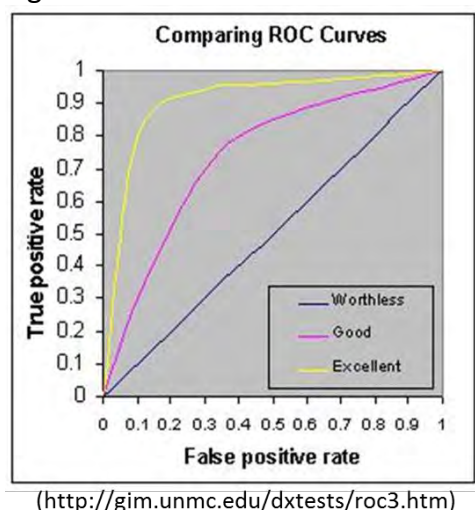
Comparing the six differing methods of quantifying adherence was novel (Chapter five). No other study has compared subjective, objective and electronic methods of measuring adherence together with therapeutic drug monitoring in a single cohort. Another strength of the study was the use of resistance as a secondary outcome. Again, this cohort had good overall adherence execution, reflective of the support at the site.(38) Most of the measures overestimated adherence, or lacked the sensitivity to identify non-adherence, with self-report achieving a median and IQR of 100% (Table 6.2). Only Wisepill data showed lower median adherence values, as anticipated for electronic devices.

These adherence measures were compared directly using univariate linear regression models to generate the area under receiver operating characteristic curves (AUC ROC). The AUC ROC quantifies the overall ability of the model to discriminate between individuals with the outcome of interest, i.e. failure or resistance, and those without. A larger AUC ROC denotes better prediction of the outcome. A ROC AUC of 1.0 would denote excellent prediction (Figure 7.2) and one of 0.5 would be worthless.

Self-report has an AUC ROC of 0.5-0.56 for both failure and resistance, so rendering this measure more or less useless for measuring outcomes. Simply asking whether a person has taken their medication or not usually results in a positive answer. Other communication

styles, using problem solving or motivational interviewing skills might improve chance of a missed dose being reported, but these were not explored here.

Figure 7.2



(<http://gim.unmc.edu/dxtests/roc3.htm>)

Both Wisepill and pharmacy refill adherence were highly predictive of virological failure (ROC AUC 0.73-0.76) and even more so of HIV-1 resistance (ROC AUC 0.82-0.91) at week 48 (Figures 6.1 and 6.2). While it was hypothesised that Wisepill data might improve outcome prediction compared to pill count data, the success of the pharmacy refill measures on predicting outcomes was unanticipated, even though the benefit of pharmacy systems in identifying those lost to care had already been shown (Chapter 4).⁽⁵⁷⁾ This finding emphasizes the importance of utilising pharmacy systems. Drug dispensing data can be used for both day to day adherence management as well as for retention tracking. Clinical staff already have experience with pharmacy systems, and data from the electronic dispensing record could be incorporated into existing clinic management tools. While use of pharmacy data requires consistent and accurate data capture, the method utilises staff and resources already in place. All clinics in the Western Cape use electronic dispensing systems. The disadvantage of pharmacy methods is that the data cannot pick up short term interruptions in treatment, and discontinuation from care would only be noted once the next pharmacy pick-up date was missed.

Wisepill data also gives an excellent reflection of adherence when used well. Improvements in the device are making it easier to use. Battery life has been prolonged to six months, so reducing days when the battery is flat/dead; and data is stored on the device when not near

a cell phone tower, to be uploaded later. All data is kept in “the cloud” and the device will continue to collect data from an individual anywhere in the country, allowing between clinic transfer without a loss of data. Experience in using the Wisepill is increasing world-wide, and data analysis tools are also improving.(62, 63) Regular automated reports of those with lapses in dosing or problem devices can be generated. Monthly pie charts of patient dosing behaviour are available for patient feedback (page 28). Data is more granular and detailed than that of pharmacy data as the device has the advantage of noting missed dosing in real-time, allowing immediate intervention. However, it still costly and regular use in a clinic setting might require extra staffing. Costs could potentially be offset by a reduction in the number of viral loads: 92% of those with adherence $\geq 85\%$ were successfully suppressed, compared to 77% of those with lower adherence in our study.

The clinic-based pill count methodology, which has been used to measure adherence in the Gugulethu cohort since 2002, was weakly predictive of failure (AUC ROC 0.64) and resistance (AUC ROC 0.67) at week 48. This measure requires the effort of the counseling team to count tablets and calculate percentage adherence since the previous visit.

Pharmacy refill measures were better predictors of virological outcomes than pill counts and could be automatically generated by ART programmes with electronic dispensing, thus saving staff time.

Early in treatment, at week 16, only pharmacy refill measures impacted on virological failure and no measure predicted HIV-1 resistance. Each adherence measure was used in a multivariate model, which included the CD4 cell count and HIV-1 RNA from baseline, as well as age. At week 16 the predictive value for the multivariate model alone (with no adherence variables included) was already very high (AUC ROC 0.88) and improved only slightly by the addition of the pharmacy refill adherence variables (AUC ROC 0.91) and not at all by the other measures. This early in treatment, knowledge of pre-treatment clinical status appears to be more important than knowledge of an individual’s adherence. However, by week 48 the increasing value of the adherence measure can be seen with 5-10% improvements in the AUC ROC with Wisepill and pharmacy refill measures. A limitation of these per-protocol analyses is that the participant required a viral load to be included in the analysis. We have no information on those who did not return to the clinic at week 16.

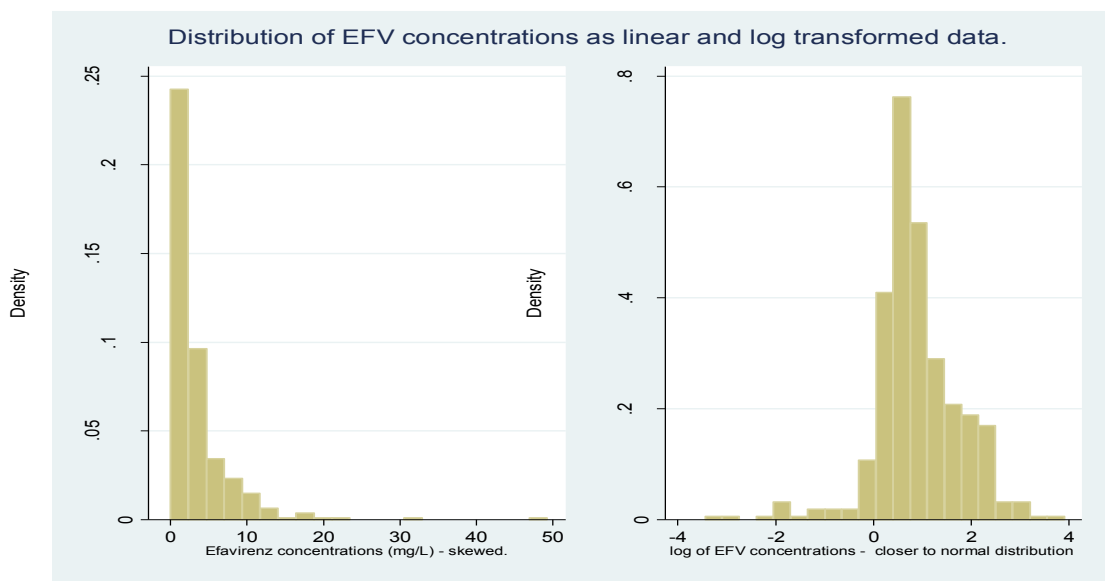
In summary, Chapters 4 and 6 show the potential of the pharmacy dispensing system in monitoring both adherence and retention outcomes and should be used more widely for both purposes. Both of the pharmacy refill adherence measures used in Chapter 6 as well as electronic adherence monitoring using the Wisepill device have the potential to predict treatment and resistance outcomes at week 48. Data from the Wisepill substantially reduced the discrepancy between adherence and virological outcome. Pharmacy refill measures and Wisepill stand out as the best options for monitoring adherence throughout.

Therapeutic drug monitoring as an adherence tool

Drug concentrations have not been used to measure adherence in any of the mobile phone intervention studies. Initial exploration in our adherence comparison paper (Chapter 6) showed that modelling EFV concentration using linear regression did not result in prediction of virological outcomes at either week 16 or 48, as most EFV concentrations were within the therapeutic range. The few individuals with drug concentrations below the limit of quantification ($n=3$) at week 48 did have worse virological outcomes when compared categorically to those with detectable efavirenz, but the confidence intervals were wide, due to the small sample size. Categorical analysis at above and below 1mg/L, the current suggested lower therapeutic threshold, however, showed no association of lower concentrations with failure (Chapter 6).

Two procedures assisted to clarify the impact of efavirenz concentration on virological outcome in Chapter 5. Log transforming the data changed the distribution to spread out the lower concentrations more likely to impact on virological outcome (Figure 7.3). The Cox proportional hazard model also allowed incorporation of both week 16 and week 48 data into one model. This model showed that efavirenz concentrations highly significantly impacted on virological outcomes (for every time efavirenz concentration doubled, the hazard of failure decreased by 21%). In addition, the efavirenz concentration below which rate of failure increased (0.7mg/L) fell in-between the lower limit of assay quantification (0.0195mg/L) and the lower end of the predicted therapeutic range (1mg/L), which fitted with the categorical analyses completed in Chapter six and described above.

Figure 7.3



Genotypic metaboliser status did not impact on virological outcome. Even in those who were extensive metabolisers, the lower inter-quartile range of drug concentration remained higher than the cut-off value of 0.7 mg/L established here. However, low efavirenz concentrations do drive virological failure. It is likely to be poor adherence that pushes the concentrations below the critical threshold, rather than metaboliser status.

The identification of drug within the body is the only means of being certain that the medication has actually been taken. All other adherence measures can be modified by the individual without drug being ingested. Our findings suggest that efavirenz therapeutic drug monitoring could be used programmatically to predict failure particularly in those with poor adherence. However, pharmacogenetic sampling, which is unaffordable, would not be required.

Novel messages

While the lack of positive impact on cumulative adherence and virological outcomes with the Wisepill text message reminder intervention was disappointing, there have been a number of novel outcomes from this work. This is the first time that text messaging has been noted to reduce treatment interruptions, a potentially important finding that can be explored further.

This was the also the first time that pharmacy refill data and electronic data were directly compared and learning that pharmacy refill is on a par with electronic methods in resource-poor settings is a crucial piece of information that should be implemented programmatically.

We have shown that in a naive cohort, contrary to prior recommendations, efavirenz therapeutic drug monitoring is a potentially useful adjunct to routine adherence measures. We have also confirmed that the lower threshold of the normal range for efavirenz is set too high and have contributed to data supporting the use of a lower dose of EFV.(165)

Strengths and limitations

There were a number of strengths to this work. It comprised a blend of observational cohort data together with more rigorously collected data from a randomised controlled trial to improve the depth of evidence on which adherence messages are based. As the characteristics of the RCT cohort in terms of demographic information, adherence and discontinuation data are comparable with those of the observational cohorts, data from the RCT can be easily generalised to the whole cohort and potentially more widely, as the Gugulethu cohort is representative of many other sub-Saharan cohorts.

The study included adherence as measured by objective and electronic methods, not only subjective methods; and, critically, presented biological outcome measures in addition to these. The RCT was completed over a 12 month period – which can be seen as a strength, as many adherence studies are of much shorter duration (See Tables 2.1, 2.4, 2.5). However, there is still a need for such detailed adherence data to be collected over a much longer time frame, as people spend more years on ART.

There were a number of study limitations. Due to the two-year window of funding for the RCT, we had to recruit rapidly (over 6 months). In order to recruit the 230 individuals needed to power the study within that time frame, a naïve cohort had to be selected. As discussed above, this seems likely to have reduced the impact of the intervention, by reducing the number of participants in the study with poor adherence and for whom the text message reminder might have had benefit. In addition, the Hannan Crusaid Treatment Centre site has been the focus of research attention relating to adherence in the past.

Multiple efforts to support adherence to ART were already in place, including pre-treatment literacy sessions, regular monitoring of objective adherence measures and a stepped-up adherence intervention should adherence drop <90% or viraemia be noted.(38)

As the study was completed in a community ART clinic, we had to be pragmatic about data collected from the clinic visits. Study-specific data, such as EFV concentrations, were collected on time. However, viral load results, other than those drawn at baseline, were taken from clinic records. This resulted in a number of data points having to be excluded from modeling analyses as timing of clinic visit (for viral load draw) and study visit (for drug level draw) did not coincide.

Lastly, we have not yet explored Wisepill data to its full advantage. The strength of this data lies in the richness of the daily dosing information available. Most outcomes in this study were compared to cumulative Wisepill adherence measures or treatment interruptions used as a categorical variable. The data will be analysed further with the assistance of a statistician with skill in non-linear mixed effects, so that we can explore the impact of actual daily dose timing on drug levels and virological outcomes.

Future research in the field of adherence

Adherence (initiation, implementation and discontinuation) remains a major obstacle to successful management of ART. Although adherence interventions in resource-poor settings have not been well researched, there are enough positive messages to suggest forward direction. There is also enough information to promote some methods of monitoring adherence i.e. electronic and pharmacy methods, and to minimise the use of others i.e. pill counts and self-report in a research setting.

In July 2015, I was invited to attend the Bill and Melinda Gates Foundation Adherence Experts Consultation in Vancouver, together with others who have research interests in the field (Appendix 3). The conclusion of this meeting was that, with the ongoing push to expand access to ART to those with higher CD4 counts, and eventually to treat all individuals at the point of HIV diagnosis, it is important to move toward differentiated care.(10, 18) Separating those who manage to take ART successfully within the first few months of treatment from those who do not would assist ART programme scale up and maximize the

benefit of adherence interventions. Identifying the poorly-adherent patients early in care, before missed visits and raised viral loads, would allow intervention prior to treatment failure and thus maintain individuals on simpler, safer and more cost-effective first-line treatment regimens (Figure 7.4).(25, 51, 53, 62)

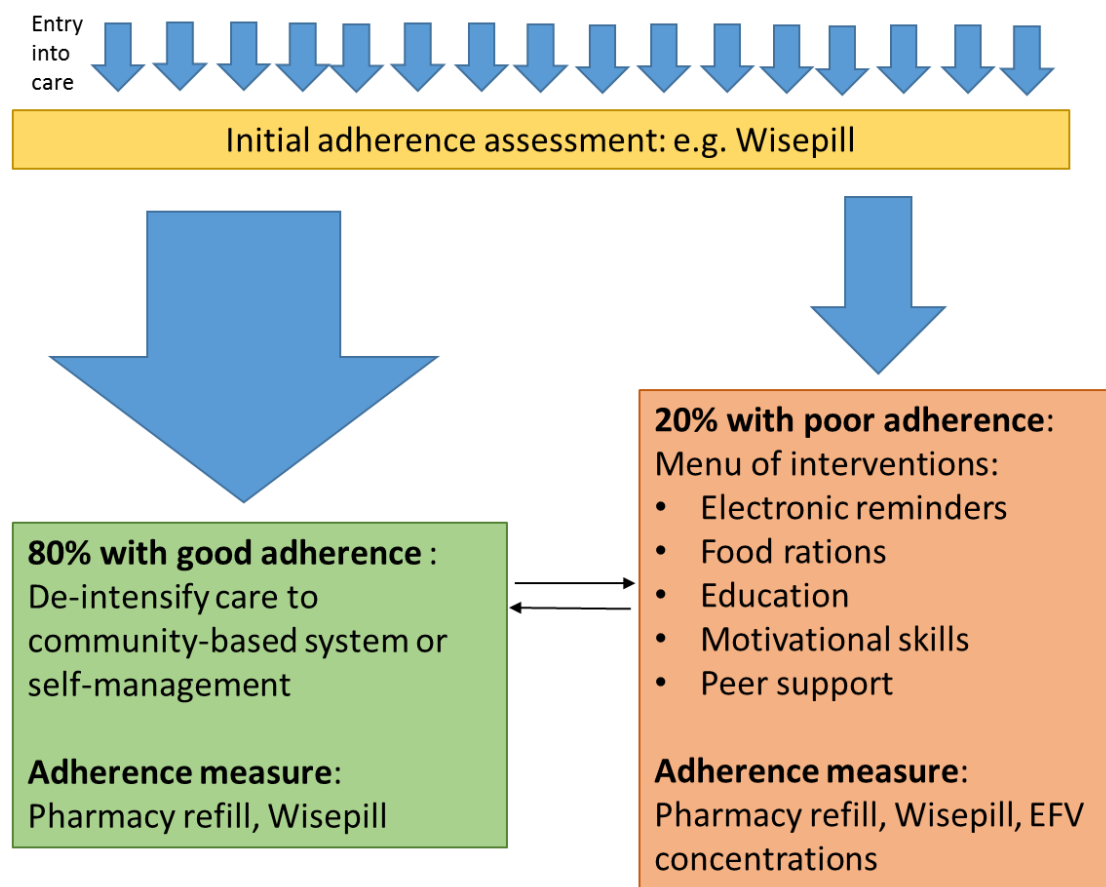
The initial identification of people who are poorly adherent within the first few weeks of treatment, while crucial, could be complex. Currently, many of those who might benefit from an adherence intervention are never identified as they discontinue ART before they reach the current first assessment point. In our setting, this is the week 16 viral load. Many who enter care are lost within these first four months.(190) In this thesis, we have shown that pharmacy refill data predicts virological outcome at week 16 and could be used to identify individuals who are late for a collection even more rapidly. However, in 16 weeks, there are at most four pharmacy collections, and an individual could have been off treatment for a month before this is noted. This is where the Wisepill device could be used for its strengths as a monitoring tool: those who miss a fourth dose could be contacted immediately [Figure 8.4]. Identifying early non-adherence then allows for exploration of reasons for poor adherence and support for the individual to improve tablet taking behaviour and develop good adherence habits.

The majority who require less care and who can establish good adherence habits early in treatment could have care delivered and adherence monitored away from a medical setting (Figure 7.4). Current planning includes task-shifting towards lay staff or community-based models of care.(13, 101, 115) However, those who self-select into this adherent group, should still have adherence monitored. As Vrijens et al. noted, life issues which impact on adherence will change over time and it cannot be assumed that once a person is adherent that their circumstance will not alter.(4) There needs to be the possibility for individuals to receive more care should their adherence falter, and similarly for individuals in the high-intensity care system to move into the down-scaled model of care.

Both of the best methods for measuring adherence, as identified in this thesis, would allow for remote monitoring of patients at any site. Wisepill uses a South Africa-wide cell phone network and data can be collected from anywhere in the country. New options for dispensing are being explored in other South African research sites e.g. an automatic drug

dispensing machine for ART is planned for areas of high population density such as shopping malls (Ian Sanne – personal communication). Pharmacy data would then also be stored in “the cloud” allowing access to medication and adherence monitoring through pharmacy refill data across the country as well. Both of the adherence measurement methodologies that we have identified as most predictive of ART outcomes can be scaled up to allow those who are well, to continue to be treated as well people, even once on ART (Figure 7.4).

Figure 7.4. Schematic of future adherence approaches.



Treatment intensification for those with poor adherence could be offered as a menu of possible interventions or a sequence of options of increasing intensity. We have shown that text reminders reduce significant treatment interruptions, and others have shown similar reminders improve cumulative adherence and virological outcomes.(50, 62, 107) Other interventions, including education and counselling methodologies, peer or family support and food parcels or other incentives could be tailored to what is available at a site, and also, within reason to the individual. For some who are forgetful, a reminder may be adequate; others with barriers such as social isolation and fears of stigma might respond to counseling

approaches; and for yet others, poverty or scarcity of food may be the major barrier. For these individuals adherence should still be monitored with some intensity, definitely using pharmacy refill measures, and possibly with electronic methods and therapeutic drug monitoring.

As we identified, some populations are at increased risk for poor adherence e.g. younger people and those with depression. However, with the use of an identification system as described above, these criteria alone do not have to label an individual as a poorly adherent. Each individual would be given the opportunity to self-identify, independent of other risk categories. These key populations may need support tailored to their needs: e.g. their own clubs, different type of text messaging or youth-friendly spaces.

More research is needed to explore classification of individuals as good or poorly adherent early in treatment. While we would suggest the best methodology would be the use of pharmacy refill data or electronic monitoring, the precise cut-off adherence point and timing of the streamlining process will need to be determined. Both simplified models of care, with adherence monitored remotely, will need to be expanded; and research into successful adherence intensification processes should be prioritised.

Policy changes

The South African ART programme and provincial clinical services need to adapt to the current challenges of ART: a growing cohort of individuals being eligible for treatment and a change in the health profile of those entering care. Based on findings of this thesis, recommendations would be to utilise pharmacy systems for program evaluations and monitoring individual adherence, including the triaging of patients early after ART initiation for streamlining of care. Locally feasible and robust options to both intensify and simplify care, including the use of electronic reminders, should be explored.

The benefit of the use of pharmacy refill methods in monitoring adherence is clear and could be acted upon immediately. The Western Cape Provincial Department of Health has rolled out the use of an electronic patient management system (eKAPA) across all of its clinics. Most clinics also have electronic dispensing systems (iDART and others), but there is no provision for the patient management system to connect with or collect data from the

pharmacy systems. At a local level, integration of the systems should be manageable and this one intervention could improve patient tracking and adherence monitoring across the Province.

7.3. Conclusion.

This thesis has examined current interventions which improve ART adherence, explored the benefits of electronic reminders, compared methods to quantitate adherence in a community ART cohort In South Africa, and established utility of EFV TDM in a community setting.

For electronic reminders, decreased frequency of messaging and the incorporating of an interactive component with a staff member seem most beneficial. Our study did not show that reminders after a missed dose improved adherence significantly, but did show that treatment interruptions were minimised, a benefit that might have had more impact had a non-naïve population been selected.

Wisepill, as an adherence monitoring tool, has the advantage of identifying missed doses rapidly and is ideal for identifying those with poor adherence and initiating immediate interventions, including text-messaging in real time.(63) Using electronic adherence monitoring may be valuable in the first few months to a year of treatment to allow streamlining of care.

Pharmacy dispensing data is an exciting and under-utilised resource. Electronic dispensing systems are in place at most clinics locally. Programmatic support should be given to incorporating the use of pharmacy data into both patient-level adherence monitoring and programme-level evaluation. Pharmacy resupply monitoring should also be used to monitor community-based treatment sites.

We found that therapeutic drug monitoring has a place in individual adherence assessment. Low EFV concentrations can predict poor virological outcomes in naïve population. Despite pharmacogenetic variation in individual EFV metabolism, this information is not required for an individual in the context of virological failure.

As we move into the second decade of ART delivery in South Africa, we need to ensure that treatment options are acceptable, effective and can be used at scale. We need to think broadly about systems to support the influx of those needing treatment who are healthy and channeling the use of our clinic and human resources to those at most need. We need flexible and robust adherence monitoring systems, such as those identified here that more closely reflect virological outcomes, to allow for differing needs by each individual and differing needs within one individual over time.

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References.

1. Johnson LF, Mossong J, Dorrington RE, Schomaker M, Hoffmann CJ, Keiser O, et al. Life expectancies of South African adults starting antiretroviral treatment: collaborative analysis of cohort studies. *PLoS medicine*. 2013;10(4):e1001418.
2. Eaton J N-MJ, Herbst K, Crampin A, Kabudula C, Urassa M, Nyaguara A, Reniers G, Slaymaker E. The Impact of Antiretroviral Therapy on Adult Life Expectancy in Sub-Saharan Africa. Conference on Retrovirus and Opportunistic Infections; 23-26th February.; Seattle2015.
3. Vrijens B, Urquhart, J., White, D. Electronically monitored dosing histories can be used to develop a medication-taking habit and manage patient adherence. *Expert Rev Clin Pharmacol*. 2014;Early on-line:1-12.
4. Vrijens B, De Geest S, Hughes DA, Przemyslaw K, Demonceau J, Ruppar T, et al. A new taxonomy for describing and defining adherence to medications. *Br J Clin Pharmacol*. 2012;73(5):691-705.
5. Thompson MA, Mugavero MJ, Amico KR, Cargill VA, Chang LW, Gross R, et al. Guidelines for improving entry into and retention in care and antiretroviral adherence for persons with HIV: evidence-based recommendations from an International Association of Physicians in AIDS Care panel. *Ann Intern Med*. 2012;156(11):817-33, w-284, w-5, w-6, w-7, w-8, w-9, w-90, w-91, w-92, w-93, w-94.
6. Shisana O, Rehle, T, Simbayi LC, Zuma, K, Jooste, S, Zungu N, Labadarios, D, Onoya, D et al. . South African National HIV Prevalence, Incidence and Behaviour Survey, 20122014 27Mar2015.
7. Africa SS. Mid-year population estimates. 2015.
8. UNAIDS. Country Report: South Africa HIV and AIDS estimates (2014) 2014 [cited 2015 12November]. Available from: <http://www.unaids.org/en/regionscountries/countries/southafrica/>.
9. Lundgren JD, Babiker AG, Gordin F, Emery S, Grund B, Sharma S, et al. Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection. *The New England journal of medicine*. 2015;373(9):795-807.
10. National consolidated guidelines for the prevention of mother-to-child transmission of HIV (PMTCT) and the management of HIV in children, adolescents and adults. <http://www.health.gov.za/policies.php>; Department of Health, Pretoria, South Africa; 2014 [updated 24 December 2014]. Available from: <http://www.health.gov.za/policies.php>.
11. Lundgren J, Babiker A., Gordin F., Neaton J.. The START study: design, conduct and main results. International AIDS Society Conference; 19th to 22nd July.; Vancouver2015.
12. Danel C, Moh R, Gabillard D, Badje A, Le Carrou J, Ouassa T, et al. A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa. *The New England journal of medicine*. 2015;373(9):808-22.
13. Grimsrud A SJ, Kalombo C, Bekker LG and Myer L. Implementation of community-based adherence clubs for stable antiretroviral therapy patients in Cape Town, South Africa. *Journal of the International AIDS Society*. 2015;18:19984.
14. Grimsrud A CM, Schomaker M, Fox MP, Orrell C, Prozesky H, Stinson K, Tanser F, Egger M, Myer L, for the International Epidemiologic Databases to Evaluate AIDS Southern Africa Collaboration (IeDEA-SA). CD4 count at antiretroviral therapy initiation and the risk of loss to follow-up: Results from a multicentre cohort study. *PloS one*. 2015;in review.
15. Adakun SA, Siedner MJ, Muzoora C, Haberer JE, Tsai AC, Hunt PW, et al. Higher baseline CD4 cell count predicts treatment interruptions and persistent viremia in patients initiating ARVs in rural Uganda. *Journal of acquired immune deficiency syndromes (1999)*. 2013;62(3):317-21.
16. Paterson DL, Swindells S, Mohr J, Brester M, Vergis EN, Squier C, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Ann Intern Med*. 2000;133(1):21-30.

17. Parienti JJ, Das-Douglas M, Massari V, Guzman D, Deeks SG, Verdon R, et al. Not all missed doses are the same: sustained NNRTI treatment interruptions predict HIV rebound at low-to-moderate adherence levels. *PLoS one*. 2008;3(7):e2783.
18. Adolescents. PoAGfAa. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. In: and DoH, Services. H, editors. Available at <http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>. 2014.
19. Orrell C, Walensky RP, Losina E, Pitt J, Freedberg KA, Wood R. HIV type-1 clade C resistance genotypes in treatment-naïve patients and after first virological failure in a large community antiretroviral therapy programme. *Antiviral therapy*. 2009;14(4):523-31.
20. Wallis CL, Aga E, Ribaudo H, Saravanan S, Norton M, Stevens W, et al. Drug susceptibility and resistance mutations after first-line failure in resource limited settings. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 2014;59(5):706-15.
21. Hosseinipour MC, van Oosterhout JJ, Weigel R, Phiri S, Kamwendo D, Parkin N, et al. The public health approach to identify antiretroviral therapy failure: high-level nucleoside reverse transcriptase inhibitor resistance among Malawians failing first-line antiretroviral therapy. *AIDS (London, England)*. 2009;23(9):1127-34.
22. Marconi VC, Sunpath H, Lu Z, Gordon M, Koranteng-Apeagyei K, Hampton J, et al. Prevalence of HIV-1 drug resistance after failure of a first highly active antiretroviral therapy regimen in KwaZulu Natal, South Africa. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 2008;46(10):1589-97.
23. G Meintjies JB, F Conradie, V Cox, S Dlamini, J Fabian, G Maartens, T Manzini, M Mathe, C Menezes, M Moorhouse, Y Moosa, J Nash CO, Y Pakade, F Venter, D Wilson for the Southern African HIV Clinicians Society. Adult antiretroviral therapy guidelines 2014. *Southern African Journal of HIV Medicine*. 2014;15(4).
24. Wallis CL, Papathanasopoulos MA, Fox M, Conradie F, Ive P, Orrell C, et al. Low rates of nucleoside reverse transcriptase inhibitor resistance in a well-monitored cohort in South Africa on antiretroviral therapy. *Antiviral therapy*. 2012;17(2):313-20.
25. Orrell C, Harling G, Lawn SD, Kaplan R, McNally M, Bekker LG, et al. Conservation of first-line antiretroviral treatment regimen where therapeutic options are limited. *Antiviral therapy*. 2007;12(1):83-8.
26. Nachega JB, Parienti JJ, Uthman OA, Gross R, Dowdy DW, Sax PE, et al. Lower pill burden and once-daily antiretroviral treatment regimens for HIV infection: A meta-analysis of randomized controlled trials. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 2014;58(9):1297-307.
27. Orrell C, Bangsberg DR, Badri M, Wood R. Adherence is not a barrier to successful antiretroviral therapy in South Africa. *AIDS (London, England)*. 2003;17(9):1369-75.
28. Mills EJ, Nachega JB, Buchan I, Orbinski J, Attaran A, Singh S, et al. Adherence to antiretroviral therapy in sub-Saharan Africa and North America: a meta-analysis. *JAMA : the journal of the American Medical Association*. 2006;296(6):679-90.
29. Bisson GP, Rowh A, Weinstein R, Gaolathe T, Frank I, Gross R. Antiretroviral failure despite high levels of adherence: discordant adherence-response relationship in Botswana. *Journal of acquired immune deficiency syndromes (1999)*. 2008;49(1):107-10.
30. Nachega JB, Marconi VC, van Zyl GU, Gardner EM, Preiser W, Hong SY, et al. HIV treatment adherence, drug resistance, virologic failure: evolving concepts. *Infectious disorders drug targets*. 2011;11(2):167-74.
31. Fox MP, Cutsem GV, Giddy J, Maskew M, Keiser O, Prozesky H, et al. Rates and predictors of failure of first-line antiretroviral therapy and switch to second-line ART in South Africa. *Journal of acquired immune deficiency syndromes (1999)*. 2012;60(4):428-37.
32. Harries AD, Zachariah R, van Oosterhout JJ, Reid SD, Hosseinipour MC, Arendt V, et al. Diagnosis and management of antiretroviral-therapy failure in resource-limited settings in sub-Saharan Africa: challenges and perspectives. *The Lancet infectious diseases*. 2010;10(1):60-5.

33. Orrell C, Kaplan R, Wood R, Bekker LG. Virological breakthrough: a risk factor for loss to followup in a large community-based cohort on antiretroviral therapy. *AIDS research and treatment*. 2011;2011:469127.
34. Boyles TH, Wilkinson LS, Leisegang R, Maartens G. Factors influencing retention in care after starting antiretroviral therapy in a rural South African programme. *PloS one*. 2011;6(5):e19201.
35. Geng EH, Glidden DV, Bwana MB, Musinguzi N, Emenyonu N, Muyindike W, et al. Retention in care and connection to care among HIV-infected patients on antiretroviral therapy in Africa: estimation via a sampling-based approach. *PloS one*. 2011;6(7):e21797.
36. Bae JW, Guyer W, Grimm K, Altice FL. Medication persistence in the treatment of HIV infection: a review of the literature and implications for future clinical care and research. *AIDS (London, England)*. 2011;25(3):279-90.
37. Kranzer K, Lewis JJ, Ford N, Zeinecker J, Orrell C, Lawn SD, et al. Treatment interruption in a primary care antiretroviral therapy program in South Africa: cohort analysis of trends and risk factors. *Journal of acquired immune deficiency syndromes (1999)*. 2010;55(3):e17-23.
38. Ncaca LN, Kranzer K, Orrell C. Treatment interruption and variation in tablet taking behaviour result in viral failure: a case-control study from Cape Town, South Africa. *PloS one*. 2011;6(8):e23088.
39. Genberg BL, Wilson IB, Bangsberg DR, Arnsten J, Goggin K, Remien RH, et al. Patterns of antiretroviral therapy adherence and impact on HIV RNA among patients in North America. *AIDS (London, England)*. 2012;26(11):1415-23.
40. Nglazi MD, Lawn SD, Kaplan R, Kranzer K, Orrell C, Wood R, et al. Changes in programmatic outcomes during 7 years of scale-up at a community-based antiretroviral treatment service in South Africa. *Journal of acquired immune deficiency syndromes (1999)*. 2011;56(1):e1-8.
41. Sinxadi PZ, Leger PD, McIlleron HM, Smith PJ, Dave JA, Levitt NS, et al. Pharmacogenetics of plasma efavirenz exposure in HIV-infected adults and children in South Africa. *Br J Clin Pharmacol*. 2015;80(1):146-56.
42. Muller AD, Jaspan HB, Myer L, Hunter AL, Harling G, Bekker LG, et al. Standard measures are inadequate to monitor pediatric adherence in a resource-limited setting. *AIDS Behav*. 2011;15(2):422-31.
43. Oyugi JH, Byakika-Tusiime J, Ragland K, Laeyendecker O, Mugerwa R, Kityo C, et al. Treatment interruptions predict resistance in HIV-positive individuals purchasing fixed-dose combination antiretroviral therapy in Kampala, Uganda. *AIDS (London, England)*. 2007;21(8):965-71.
44. Marcellin F, Spire B, Carrieri MP, Roux P. Assessing adherence to antiretroviral therapy in randomized HIV clinical trials: a review of currently used methods. *Expert Rev Anti Infect Ther*. 2013;11(3):239-50.
45. Simoni JM, Kurth AE, Pearson CR, Pantalone DW, Merrill JO, Frick PA. Self-report measures of antiretroviral therapy adherence: A review with recommendations for HIV research and clinical management. *AIDS Behav*. 2006;10(3):227-45.
46. Wagner G, Miller LG. Is the influence of social desirability on patients' self-reported adherence overrated? *Journal of acquired immune deficiency syndromes (1999)*. 2004;35(2):203-4.
47. Williams AB, Amico KR, Bova C, Womack JA. A proposal for quality standards for measuring medication adherence in research. *AIDS Behav*. 2013;17(1):284-97.
48. Chesney MA IJ, Chambers DB et al. Patient Care Committee & Adherence Working Group of the Outcomes Committee of the Adult AIDS Clinical Trials Group (AACTG). . Self-reported adherence to antiretroviral medications among participants in HIV clinical trials: the AACTG adherence instruments. . *AIDS Care - Psychological and Socio-Medical Aspects of AIDS/HIV*. 2000;12(3):255-66.
49. Glass T, Cavassini M. Asking about adherence - from flipping the coin to strong evidence. *Swiss medical weekly*. 2014;144:w14016.

50. Lester RT, Ritvo P, Mills EJ, Kariri A, Karanja S, Chung MH, et al. Effects of a mobile phone short message service on antiretroviral treatment adherence in Kenya (WelTel Kenya1): a randomised trial. *Lancet*. 2010;376(9755):1838-45.
51. Hardy H, Kumar V, Doros G, Farmer E, Drainoni ML, Rybin D, et al. Randomized controlled trial of a personalized cellular phone reminder system to enhance adherence to antiretroviral therapy. *AIDS patient care and STDs* [Internet]. 2011; 25(3):[153-61 pp.]. Available from: <http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/497/CN-00787497/frame.html>
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3101947/pdf/apc.2010.0006.pdf>.
52. Da Costa TM, Barbosa BJP, E Costa DAG, Sigulem D, De Fátima Marin H, Filho AC, et al. Results of a randomized controlled trial to assess the effects of a mobile SMS-based intervention on treatment adherence in HIV/AIDS-infected Brazilian women and impressions and satisfaction with respect to incoming messages. *International Journal of Medical Informatics*. 2012;81(4):257-69.
53. Maduka O, Obin-West CI. Adherence counseling and reminder text messages improve uptake of antiretroviral therapy in a tertiary hospital in Nigeria. *Nigerian Journal of Clinical Practice* [Internet]. 2013; 16(3):[302-8 pp.]. Available from: <http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/551/CN-00918551/frame.html>.
54. Gill CJ, Hamer DH, Simon JL, Thea DM, Sabin LL. No room for complacency about adherence to antiretroviral therapy in sub-Saharan Africa. *AIDS (London, England)*. 2005;19(12):1243-9.
55. Wu P, Johnson BA, Nachega JB, Wu B, Ordonez CE, Hare AQ, et al. The combination of pill count and self-reported adherence is a strong predictor of first-line ART failure for adults in South Africa. *Current HIV research*. 2014;12(5):366-75.
56. Deschamps AE, De Geest S, Vandamme AM, Bobbaers H, Peetermans WE, Van Wijngaerden E. Diagnostic value of different adherence measures using electronic monitoring and virologic failure as reference standards. *AIDS patient care and STDs*. 2008;22(9):735-43.
57. Nachega JB, Hislop M, Dowdy DW, Lo M, Omer SB, Regensberg L, et al. Adherence to highly active antiretroviral therapy assessed by pharmacy claims predicts survival in HIV-infected South African adults. *Journal of acquired immune deficiency syndromes (1999)*. 2006;43(1):78-84.
58. Court R, Leisegang R, Stewart A, Sunpath H, Murphy R, Winternheimer P, et al. Short term adherence tool predicts failure on second line protease inhibitor-based antiretroviral therapy: an observational cohort study. *BMC infectious diseases*. 2014;14(1):664.
59. Bisson GP, Gross R, Bellamy S, Chittams J, Hislop M, Regensberg L, et al. Pharmacy refill adherence compared with CD4 count changes for monitoring HIV-infected adults on antiretroviral therapy. *PLoS medicine*. 2008;5(5):e109.
60. Haberer JE, Kahane J, Kigozi I, Emenyonu N, Hunt P, Martin J, et al. Real-time adherence monitoring for HIV antiretroviral therapy. *AIDS Behav*. 2010;14(6):1340-6.
61. Oyugi JH, Byakika-Tusiime J, Charlebois ED, Kityo C, Mugerwa R, Mugenyi P, et al. Multiple validated measures of adherence indicate high levels of adherence to generic HIV antiretroviral therapy in a resource-limited setting. *Journal of acquired immune deficiency syndromes (1999)*. 2004;36(5):1100-2.
62. Sabin LL, Bachman DeSilva M, Gill CJ, Zhong L, Vian T, Wubin X, et al. Improving Adherence to Antiretroviral Therapy with Triggered Real Time Text Message Reminders: the China through Technology Study (CATS). *Journal of acquired immune deficiency syndromes (1999)*. 2015; 69(5):551-9.
63. Haberer JE, Kiwanuka J, Nansera D, Muzoora C, Hunt PW, So J, et al. Realtime adherence monitoring of antiretroviral therapy among HIV-infected adults and children in rural Uganda. *AIDS (London, England)*. 2013;27(13):2166-8.
64. Liu X, Ma Q, Zhang F. Therapeutic drug monitoring in highly active antiretroviral therapy. *Expert opinion on drug safety*. 2010;9(5):743-58.

65. Kredt T, Van der Walt J-S, Siegfried N, Cohen K. Therapeutic drug monitoring of antiretrovirals for people with HIV. Cochrane Database of Systematic Reviews [Internet]. 2009; (3). Available from: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD007268.pub2/abstract>.
66. Grant RM, Anderson PL, McMahan V, Liu A, Amico KR, Mehrotra M, et al. Uptake of pre-exposure prophylaxis, sexual practices, and HIV incidence in men and transgender women who have sex with men: a cohort study. *The Lancet infectious diseases*. 2014;14(9):820-9.
67. Grant RM, Lama JR, Anderson PL, McMahan V, Liu AY, Vargas L, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *The New England journal of medicine*. 2010;363(27):2587-99.
68. Back D, Gatti G, Fletcher C, Garaffo R, Haubrich R, Hoetelmans R, et al. Therapeutic drug monitoring in HIV infection: current status and future directions. *AIDS (London, England)*. 2002;16 Suppl 1(1):S5-37.
69. Cohen K, Grant A, Dandara C, McIlleron H, Pemba L, Fielding K, et al. Effect of rifampicin-based antitubercular therapy and the cytochrome P450 2B6 516G>T polymorphism on efavirenz concentrations in adults in South Africa. *Antiviral therapy*. 2009;14(5):687-95.
70. McIlleron HM, Schomaker M, Ren Y, Sinxadi P, Nuttall JJ, Gous H, et al. Effects of rifampin-based antituberculosis therapy on plasma efavirenz concentrations in children vary by CYP2B6 genotype. *AIDS (London, England)*. 2013;27(12):1933-40.
71. Lee SS, To KW, Lee MP, Wong NS, Chan DP, Li PC, et al. Sleep quality in efavirenz-treated Chinese HIV patients - comparing between GT and GG genotype of CYP2B6-516 G/T polymorphisms. *International journal of STD & AIDS*. 2014;25(3):193-200.
72. Gandhi M, Yang Q, Bacchetti P, Huang Y. Short communication: A low-cost method for analyzing nevirapine levels in hair as a marker of adherence in resource-limited settings. *AIDS research and human retroviruses*. 2014;30(1):25-8.
73. Gandhi M, Ameli N, Bacchetti P, Gange SJ, Anastos K, Levine A, et al. Protease inhibitor levels in hair strongly predict virologic response to treatment. *AIDS (London, England)*. 2009;23(4):471-8.
74. Prasitsuebsai W, Kerr SJ, Truong KH, Anaworanich J, Do VC, Nguyen LV, et al. Using lopinavir concentrations in hair samples to assess treatment outcomes on second-line regimens among Asian children. [AIDS Res Hum Retroviruses](#). 2015 Oct;31(10):1009-14.
75. Gandhi M, Glidden DV, Liu A, Anderson PL, Horng H, Defechereuz P, et al. Strong Correlation Between Concentrations of Tenofovir (TFV) Emtricitabine (FTC) in Hair and TFV Diphosphate and FTC Triphosphate in Dried Blood Spots in the iPrEx Open Label Extension: Implications for Pre-exposure Prophylaxis Adherence Monitoring. [J Infect Dis](#). 2015 Nov 1;212(9):1402-6.
76. Orrell C, Cohen K, Conradie F, Zeinecker J, Ive P, Sanne I, et al. Efavirenz and rifampicin in the South African context: is there a need to dose-increase efavirenz with concurrent rifampicin therapy? *Antiviral therapy*. 2011;16(4):527-34.
77. Kaplan R, Orrell C, Zwane E, Bekker LG, Wood R. Loss to follow-up and mortality among pregnant women referred to a community clinic for antiretroviral treatment. *AIDS (London, England)*. 2008;22(13):1679-81.
78. Bonner K, Mezocho A, Roberts T, Ford N, Cohn J. Viral load monitoring as a tool to reinforce adherence: a systematic review. *Journal of acquired immune deficiency syndromes (1999)*. 2013;64(1):74-8.
79. Liu H, Golin CE, Miller LG, Hays RD, Beck CK, Sanandaji S, et al. A comparison study of multiple measures of adherence to HIV protease inhibitors. *Ann Intern Med*. 2001;134(10):968-77.
80. Njuguna C, Orrell C, Kaplan R, Bekker LG, Wood R, Lawn SD. Rates of switching antiretroviral drugs in a primary care service in South Africa before and after introduction of tenofovir. *PloS one*. 2013;8(5):e63596.

81. Sanne I, Orrell C, Fox MP, Conradie F, Ive P, Zeinecker J, et al. Nurse versus doctor management of HIV-infected patients receiving antiretroviral therapy (CIPRA-SA): a randomised non-inferiority trial. *Lancet*. 2010;376(9734):33-40.
82. Keiser O, Orrell C, Egger M, Wood R, Brinkhof MW, Furrer H, et al. Public-health and individual approaches to antiretroviral therapy: township South Africa and Switzerland compared. *PLoS medicine*. 2008;5(7):e148.
83. Keiser O, Chi BH, Gsponer T, Boulle A, Orrell C, Phiri S, et al. Outcomes of antiretroviral treatment in programmes with and without routine viral load monitoring in Southern Africa. *AIDS (London, England)*. 2011;25(14):1761-9.
84. Wood R KR, Bekker LG, Brown S, Rivett U. The utility of pharmacy dispensing data for ART programme evaluation and early identification of patients lost to follow-up. *The Southern African Journal of HIV Medicine*. 2008;9:44-8.
85. Gapminder. Bubble map of cell phones (per 100 people). 2010 [cited 26August2015 26August2015]. Available from: [http://www.gapminder.org/world/#\\$majorMode=chart\\$;is:shi=t;ly=2003;lb=f;il=t;fs=11;al=30;stl=t;st=t;nsi=t;se=t\\$wst;ts=C\\$;sp=5.59290322580644;ti=2010\\$zpv:v=0\\$inc_x:mmid=XCOORDS;iid=phAwcNAVuyj1jiMAkmq1iMg;by=ind\\$inc_y:mmid=YCOORDS;iid=0AkBd6lyS3EmpdG1MSjEyS0h2QjRQZ3FXRVR2dVQyeFE;by=ind\\$inc_s:uniValue=8.21;iid=phAwcNAVuyj0XOOBL_n5tAQ;by=ind\\$inc_c:uniValue=255;qid=CATID0;by=grp\\$map_x:scale=log;dataMin=194;dataMax=96846\\$map_y:scale=lin;dataMin=0;dataMax=243\\$map_s:sma=50;smi=2\\$cd:bd=0\\$inds=i209_t002010](http://www.gapminder.org/world/#$majorMode=chart$;is:shi=t;ly=2003;lb=f;il=t;fs=11;al=30;stl=t;st=t;nsi=t;se=t$wst;ts=C$;sp=5.59290322580644;ti=2010$zpv:v=0$inc_x:mmid=XCOORDS;iid=phAwcNAVuyj1jiMAkmq1iMg;by=ind$inc_y:mmid=YCOORDS;iid=0AkBd6lyS3EmpdG1MSjEyS0h2QjRQZ3FXRVR2dVQyeFE;by=ind$inc_s:uniValue=8.21;iid=phAwcNAVuyj0XOOBL_n5tAQ;by=ind$inc_c:uniValue=255;qid=CATID0;by=grp$map_x:scale=log;dataMin=194;dataMax=96846$map_y:scale=lin;dataMin=0;dataMax=243$map_s:sma=50;smi=2$cd:bd=0$inds=i209_t002010).
86. Bank TW. Updated Income Classifications 2015 [cited 2015 16 November]. Available from: <http://data.worldbank.org/news/2015-country-classifications>.
87. Idoko JA, Agbaji O, Agaba P, Akolo C, Inuwa B, Hassan Z, et al. Direct observation therapy-highly active antiretroviral therapy in a resource-limited setting: the use of community treatment support can be effective. *International journal of STD & AIDS*. 2007;18(11):760-3.
88. Munoz M, Finnegan K, Zeladita J, Caldas A, Sanchez E, Callacna M, et al. Community-based DOT-HAART accompaniment in an urban resource-poor setting. *AIDS Behav*. 2010;14(3):721-30.
89. Nachega JB, Chaisson RE, Goliath R, Efron A, Chaudhary MA, Ram M, et al. Randomized controlled trial of trained patient-nominated treatment supporters providing partial directly observed antiretroviral therapy. *AIDS (London, England)*. 2010;24(9):1273-80.
90. Pearson CR, Micek MA, Simoni JM, Hoff PD, Matediana E, Martin DP, et al. Randomized control trial of peer-delivered, modified directly observed therapy for HAART in Mozambique. *Journal of acquired immune deficiency syndromes (1999)*. 2007;46(2):238-44.
91. Sarna A, Luchters S, Geibel S, Chersich MF, Munyao P, Kaai S, et al. Short- and long-term efficacy of modified directly observed antiretroviral treatment in Mombasa, Kenya: a randomized trial. *Journal of acquired immune deficiency syndromes (1999)*. 2008;48(5):611-9.
92. Mansoor LE, Dowse R. Medicines information and adherence in HIV/AIDS patients. *Journal of clinical pharmacy and therapeutics*. 2006;31(1):7-15.
93. Oligbu G BO, Ashom D, Adeyemi A. Effect of structured systematic teaching of HIV/AIDS patients on adherence to HAART: report from a National HIV/AIDS Treatment Centre in sub-Saharan Africa. 4th International Conference on HIV Treatment Adherence; April 5-7.; Miami, Florida2009.
94. Sampaio-Sa M, Page-Shafer K, Bangsberg DR, Evans J, Dourado Mde L, Teixeira C, et al. 100% adherence study: educational workshops vs. video sessions to improve adherence among ART-naïve patients in Salvador, Brazil. *AIDS Behav*. 2008;12(4 Suppl):S54-62.
95. van Loggerenberg F, Grant AD, Naidoo K, Murrman M, Gengiah S, Gengiah TN, et al. Individualised motivational counselling to enhance adherence to antiretroviral therapy is not superior to didactic counselling in South African patients: findings of the CAPRISA 058 randomised controlled trial. *AIDS Behav*. 2015;19(1):145-56.

96. Chang LW, Kagaayi J, Nakigozi G, Ssempijja V, Packer AH, Serwadda D, et al. Effect of peer health workers on AIDS care in Rakai, Uganda: a cluster-randomized trial. *PloS one*. 2010;5(6):e10923.
97. Munoz M, Bayona J, Sanchez E, Arevalo J, Sebastian JL, Arteaga F, et al. Matching social support to individual needs: a community-based intervention to improve HIV treatment adherence in a resource-poor setting. *AIDS Behav*. 2011;15(7):1454-64.
98. Mugusi F, Mugusi S, Bakari M, Hejdemann B, Josiah R, Janabi M, et al. Enhancing adherence to antiretroviral therapy at the HIV clinic in resource constrained countries; the Tanzanian experience. *Tropical medicine & international health : TM & IH*. 2009;14(10):1226-32.
99. Taiwo BO, Idoko JA, Welty LJ, Otoh I, Job G, Iyaji PG, et al. Assessing the virologic and adherence benefits of patient-selected HIV treatment partners in a resource-limited setting. *Journal of acquired immune deficiency syndromes (1999)*. 2010;54(1):85-92.
100. Batavia AS, Balaji K, Houle E, Parisaboina S, Ganesh AK, Mayer KH, et al. Adherence to antiretroviral therapy in patients participating in a graduated cost recovery program at an HIV care center in South India. *AIDS Behav*. 2010;14(4):794-8.
101. Kipp W, Konde-Lule J, Saunders LD, Alibhai A, Houston S, Rubaale T, et al. Results of a community-based antiretroviral treatment program for HIV-1 infection in Western Uganda. *Current HIV research*. 2010;8(2):179-85.
102. Matovu F WD, Nakibuuka J, Mabiru M, Bagenda D, Musoke P, Fowler MG. Efficacy of using peer counselors and nurses to support adherence to HAART among Ugandan HIV-1-infected patients at the Prevention of MTCT Programme: A randomised non-inferiority intervention trial. *Conference on Retroviruses and Opportunistic Infection*; 27 Feb to 03 Mar; Boston 2011.
103. Zachariah R, Teck R, Buhendwa L, Fitzerland M, Labana S, Chinji C, et al. Community support is associated with better antiretroviral treatment outcomes in a resource-limited rural district in Malawi. *Transactions of the Royal Society of Tropical Medicine and Hygiene*. 2007;101(1):79-84.
104. Cantrell RA, Sinkala M, Megazinni K, Lawson-Marriott S, Washington S, Chi BH, et al. A pilot study of food supplementation to improve adherence to antiretroviral therapy among food-insecure adults in Lusaka, Zambia. *Journal of acquired immune deficiency syndromes (1999)*. 2008;49(2):190-5.
105. Serrano C, Laporte R, Ide M, Nouhou Y, de Truchis P, Rouveix E, et al. Family nutritional support improves survival, immune restoration and adherence in HIV patients receiving ART in developing country. *Asia Pacific journal of clinical nutrition*. 2010;19(1):68-75.
106. Chung MH, Richardson BA, Tapia K, Benki-Nugent S, Kiarie JN, Simoni JM, et al. A randomized controlled trial comparing the effects of counseling and alarm device on HAART adherence and virologic outcomes. *PLoS medicine*. 2011;8(3):e1000422.
107. Pop-Eleches C, Thirumurthy H, Habyarimana JP, Zivin JG, Goldstein MP, de Walque D, et al. Mobile phone technologies improve adherence to antiretroviral treatment in a resource-limited setting: a randomized controlled trial of text message reminders. *AIDS (London, England)*. 2011;25(6):825-34.
108. Uzma Q, Emmanuel F, Ather U, Zaman S. Efficacy of Interventions for Improving Antiretroviral Therapy Adherence in HIV/AIDS Cases at PIMS, Islamabad. *Journal of the International Association of Physicians in AIDS Care (Chicago, Ill : 2002)*. 2011;10(6):373-83.
109. Sabin LL, DeSilva MB, Hamer DH, Xu K, Zhang J, Li T, et al. Using electronic drug monitor feedback to improve adherence to antiretroviral therapy among HIV-positive patients in China. *AIDS and behavior [Internet]*. 2010; 14(3):[580-9 pp.]. Available from: <http://onlinelibrary.wiley.com/doi/cochrane/clcentral/articles/447/CN-00750447/frame.html>.
110. World Health Organisation. Consolidated guidelines on the use of Antiretroviral Drugs for treating and preventing HIV infection - recommendations for a public health approach. Geneva:June 2013.

111. Chaiyachati KH, Ogbuonji O, Price M, Suthar AB, Negussie EK, Barnighausen T. Interventions to improve adherence to antiretroviral therapy: a rapid systematic review. *AIDS* (London, England). 2014;28 Suppl 2:S187-204.
112. Barnighausen T, Chaiyachati K, Chimbindi N, Peoples A, Haberer J, Newell ML. Interventions to increase antiretroviral adherence in sub-Saharan Africa: a systematic review of evaluation studies. *The Lancet infectious diseases*. 2011;11(12):942-51.
113. Mbuagbaw L, Sivaramalingam B, Navarro T, Hobson N, Keepanasseril A, Wilczynski NJ, et al. Interventions for Enhancing Adherence to Antiretroviral Therapy (ART): A Systematic Review of High Quality Studies. *AIDS patient care and STDs*. 2015;29(5):248-66.
114. Hart JE, Jeon CY, Ivers LC, Behforouz HL, Caldas A, Drobac PC, et al. Effect of directly observed therapy for highly active antiretroviral therapy on virologic, immunologic, and adherence outcomes: a meta-analysis and systematic review. *Journal of acquired immune deficiency syndromes (1999)*. 2010;54(2):167-79.
115. Decroo T, Koole O, Remartinez D, dos Santos N, Dezembro S, Jofrisse M, et al. Four-year retention and risk factors for attrition among members of community ART groups in Tete, Mozambique. *Tropical medicine & international health : TM & IH*. 2014;19(5):514-21.
116. Fairall L, Bachmann MO, Lombard C, Timmerman V, Uebel K, Zwarenstein M, et al. Task shifting of antiretroviral treatment from doctors to primary-care nurses in South Africa (STRETCH): a pragmatic, parallel, cluster-randomised trial. *Lancet*. 2012;380(9845):889-98.
117. Huang D, Sangthong R, McNeil E, Chongsuvivatwong V, Zheng W, Yang X. Effects of a Phone Call Intervention to Promote Adherence to Antiretroviral Therapy and Quality of Life of HIV/AIDS Patients in Baoshan, China: A Randomized Controlled Trial. *AIDS research and treatment*. 2013;2013:580974.
118. Collier AC, Ribaudo H, Mukherjee AL, Feinberg J, Fischl MA, Chesney M. A randomized study of serial telephone call support to increase adherence and thereby improve virologic outcome in persons initiating antiretroviral therapy. *The Journal of infectious diseases*. 2005;192(8):1398-406.
119. Finitsis DJ, Pellowski JA, Johnson BT. Text message intervention designs to promote adherence to antiretroviral therapy (ART): a meta-analysis of randomized controlled trials. *PloS one*. 2014;9(2):e88166.
120. Mbuagbaw L, Van Der Kop ML, Lester RT, Thirumurthy H, Pop-Eleches C, Ye C, et al. Mobile phone text messages for improving adherence to antiretroviral therapy (ART): An individual patient data meta-analysis of randomised trials. *BMJ Open*. 2013 Dec 17;3(12):e003950.
121. Horvath T, Azman H, Kennedy Gail E, Rutherford George W. Mobile phone text messaging for promoting adherence to antiretroviral therapy in patients with HIV infection. *Cochrane Database of Systematic Reviews* [Internet]. 2012; (3). Available from: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD009756/abstract>.
122. Kannisto KA, Koivunen MH, Valimaki MA. Use of mobile phone text message reminders in health care services: a narrative literature review. *J Med Internet Res*. 2014;16(10):e222.
123. Bassett IV, Giddy J, Chaisson CE, Ross D, Bogart LM, Coleman SM, et al. A randomized trial to optimize HIV/TB care in South Africa: design of the Sizanani trial. *BMC infectious diseases*. 2013;13:390.
124. Mwapasa V, Pro G, Chinkhumba J, Mukaka M, Kobayashi E, Stuart A, et al. Mother-infant pair clinic and SMS messaging as innovative strategies for improving access to and retention in eMTCT care and Option B+ in Malawi: a cluster randomized control trial (the PRIME study). *Journal of acquired immune deficiency syndromes (1999)*. 2014;67 Suppl 2:S120-4.
125. Kurth A, Kuo I, Peterson J, Azikiwe N, Bazerman L, Cates A, et al. Information and Communication Technology to Link Criminal Justice Reentrants to HIV Care in the Community. *AIDS research and treatment*. 2013;2013:547381.
126. Curioso WH, Quistberg DA, Cabello R, Gozzer E, Garcia PJ, Holmes KK, et al. "It's time for your life": How should we remind patients to take medicines using short text

- messages? AMIA Annual Symposium proceedings / AMIA Symposium AMIA Symposium. 2009;2009:129-33.
127. Reynolds NR, Testa MA, Su M, Chesney MA, Neidig JL, Frank I, et al. Telephone support to improve antiretroviral medication adherence: a multisite, randomized controlled trial. *Journal of acquired immune deficiency syndromes (1999)*. 2008;47(1):62-8.
 128. Ammassari A, Trotta MP, Shalev N, Tettoni MC, Maschi S, Di Sora F, et al. Timed short messaging service improves adherence and virological outcomes in HIV-1-infected patients with suboptimal adherence to antiretroviral therapy. *Journal of acquired immune deficiency syndromes (1999)*. 2011;58(4):e113-5.
 129. Molassiotis A, Lopez-Nahas V, Chung WY, Lam SW. A pilot study of the effects of a behavioural intervention on treatment adherence in HIV-infected patients. *AIDS care*. 2003;15(1):125-35.
 130. J.M. Ikeda RB, J.B. Lopez Lopez, N. Hearst. . SMS messaging improves treatment outcome among the HIV-positive Mayan population in rural Guatemala. XIX International AIDS Conference; 22–27 July 2012; Washington DC2012.
 131. Musser D. The effect of a technology-linking care intervention on HIV/AIDS patients therapeutic drug regimen adherence. [Unpublished doctoral dissertation.]. In press.
 132. Bigna JJ, Noubiap JJ, Kouanfack C, Plottel CS, Koulla-Shiro S. Effect of mobile phone reminders on follow-up medical care of children exposed to or infected with HIV in Cameroon (MORE CARE): a multicentre, single-blind, factorial, randomised controlled trial. *The Lancet infectious diseases*. 2014;14(7):600-8.
 133. Mbuagbaw L, Thabane L, Ongolo-Zogo P, Lester RT, Mills EJ, Smieja M, et al. The Cameroon Mobile Phone SMS (CAMPS) trial: a randomized trial of text messaging versus usual care for adherence to antiretroviral therapy. *PloS one*. 2012;7(12):e46909.
 134. Orrell C CK, Mauff K, Bangsberg D, Maartens G, Wood R. . A randomised controlled trial of real-time electronic adherence monitoring with text message dosing reminders in people starting first-line antiretroviral therapy. *JAIDS*. 2015;in press.
 135. Shet A DCA, Kumarasamy N, Rodrigues R, Rewari BB, Ashorn P, Eriksson B, Diwan V, and HIVIND study team. Effect of mobile telephone reminders on treatment outcome in HIV: evidence from a randomised controlled trial in India. *British Medical Journal*. 2014;349:g5978.
 136. Ahoua L, Guenther G, Rouzioux C, Pinoges L, Anguzu P, Taburet A, et al. Immunovirological response to combined antiretroviral therapy and drug resistance patterns in children: 1- and 2-year outcomes in rural Uganda. *BMC pediatrics*. 2011;11.
 137. Simoni JM, Huh D, Frick PA, Pearson CR, Andrasik MP, Dunbar PJ, et al. Peer support and pager messaging to promote antiretroviral modifying therapy in Seattle: a randomized controlled trial. *Journal of acquired immune deficiency syndromes (1999)* [Internet]. 2009; 52(4):[465-73 pp.]. Available from: <http://onlinelibrary.wiley.com/doi/10.1002/ja.1234>.
 138. Safren SA, Hendriksen ES, Desousa N, Boswell SL, Mayer KH. Use of an on-line pager system to increase adherence to antiretroviral medications. *AIDS care*. 2003;15(6):787-93.
 139. Bigna JJ, Kouanfack C, Noubiap JJ, Plottel CS, Koulla-Shiro S. A randomized blinded controlled trial of mobile phone reminders on the follow-up medical care of HIV-exposed and HIV-infected children in Cameroon: study protocol (MORE CARE). *Trials*. 2013;14:313.
 140. Nglazi MD, Kaplan R, Wood R, Bekker LG, Lawn SD. Identification of losses to follow-up in a community-based antiretroviral therapy clinic in South Africa using a computerized pharmacy tracking system. *BMC infectious diseases*. 2010;10:329.
 141. Grimsrud A, Kaplan R, Bekker LG, Myer L. Outcomes of a nurse-managed service for stable HIV-positive patients in a large South African public sector antiretroviral therapy programme. *Tropical medicine & international health : TM & IH*. 2014;19(9):1029-39.

142. Mills EJ, Nachega JB, Bangsberg DR, Singh S, Rachlis B, Wu P, et al. Adherence to HAART: a systematic review of developed and developing nation patient-reported barriers and facilitators. *PLoS medicine*. 2006;3(11):e438.
143. Wikipedia. List of countries by mobile phones in use. Wikipedia2014 [updated 24November2014; cited 2014 02 December]. Available from: http://en.wikipedia.org/wiki/List_of_countries_by_number_of_mobile_phones_in_use
144. Pop-Eleches C, Thirumurthy H, Habyarimana JP, Zivin JG, Goldstein MP, Walque D, et al. Mobile phone technologies improve adherence to antiretroviral treatment in a resource-limited setting: a randomized controlled trial of text message reminders. *AIDS (London, England)* [Internet]. 2011; 25(6):[825-34 pp.]. Available from: <http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/025/CN-00785025/frame.html>.
145. Bigna JJR, Kouanfack C, Noubiap JJN, Plottel CS, Koulla-Shiro S. A randomized blinded controlled trial of mobile phone reminders on the follow-up medical care of HIV-exposed and HIV-infected children in Cameroon: Study protocol (MORE CARE). *Trials* [Internet]. 2013; 14(1). Available from: <http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/143/CN-00914143/frame.html>.
146. National Department of Health South Africa. Clinical Guidelines For The Management Of HIV & AIDS In Adults And Adolescents.2010 (April). Available from: <http://www.doh.gov.za/docs/>.
147. National Institute on Alcohol Abuse and Alcoholism. CAGE questionnaire <http://pubs.niaaa.nih.gov/publications/inscage.htm2002>. Available from: <http://pubs.niaaa.nih.gov/publications/inscage.htm>.
148. Herrmann C. International experiences with the Hospital Anxiety and Depression Scale--a review of validation data and clinical results. *Journal of psychosomatic research*. 1997;42(1):17-41.
149. Bernadt MW, Mumford J, Taylor C, Smith B, Murray RM. Comparison of questionnaire and laboratory tests in the detection of excessive drinking and alcoholism. *Lancet*. 1982;1(8267):325-8.
150. Wisepill technologies: real time adherence management http://reports.mediscern.com/wisepill/index.php?option=com_content&view=article&id=84:the-wisepill-dispenser2014 [cited 2014, 02 December]. Available from: http://reports.mediscern.com/wisepill/index.php?option=com_content&view=article&id=84:the-wisepill-dispenser.
151. Dybul M, Nies-Kraske E, Daucher M, Hertogs K, Hallahan CW, Csako G, et al. Long-cycle structured intermittent versus continuous highly active antiretroviral therapy for the treatment of chronic infection with human immunodeficiency virus: effects on drug toxicity and on immunologic and virologic parameters. *The Journal of infectious diseases*. 2003;188(3):388-96.
152. Lima VD, Bangsberg DR, Harrigan PR, Deeks SG, Yip B, Hogg RS, et al. Risk of viral failure declines with duration of suppression on highly active antiretroviral therapy irrespective of adherence level. *Journal of acquired immune deficiency syndromes (1999)*. 2010;55(4):460-5.
153. Rosenblum M, Deeks SG, van der Laan M, Bangsberg DR. The risk of virologic failure decreases with duration of HIV suppression, at greater than 50% adherence to antiretroviral therapy. *PloS one*. 2009;4(9):e7196.
154. Nglazi MD, Kaplan R, Orrell C, Myer L, Wood R, Bekker LG, et al. Increasing transfers-out from an antiretroviral treatment service in South Africa: patient characteristics and rates of virological non-suppression. *PloS one*. 2013;8(3):e57907.
155. Petersen ML, Wang Y, van der Laan MJ, Guzman D, Riley E, Bangsberg DR. Pillbox organizers are associated with improved adherence to HIV antiretroviral therapy and viral suppression: a marginal structural model analysis. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 2007;45(7):908-15.
156. Williams AB, Fennie KP, Bova CA, Burgess JD, Danvers KA, Dieckhaus KD. Home visits to improve adherence to highly active antiretroviral therapy: a randomized controlled trial. *Journal of acquired immune deficiency syndromes (1999)* [Internet]. 2006; 42(3):[314-

21 pp.]. Available from: <http://onlinelibrary.wiley.com/doi/10.1002/clc.12111>

157. Fenerty SD, West C, Davis SA, Kaplan SG, Feldman SR. The effect of reminder systems on patients' adherence to treatment. *Patient Prefer Adherence*. 2012;6:127-35.
158. Jones KR, Lekhak N, Kaewluang N. Using mobile phones and short message service to deliver self-management interventions for chronic conditions: A meta-review. *Worldviews on Evidence-Based Nursing*. 2014;11(2):81-8.
159. World Health Organisation UaU, . Global HIV/AIDS Response: Epidemic update and health sector progress towards universal access. Progress report 2011. Accessed 07 December 2015. Available from: <http://www.afro.who.int/en/clusters-a-programmes/dpc/acquired-immune-deficiency-syndrome/features/3439-global-hiv-aids-response-progress-report-2011.html>.
160. Douglas GP, Gadabu OJ, Joukes S, Mumba S, McKay MV, Ben-Smith A, et al. Using touchscreen electronic medical record systems to support and monitor national scale-up of antiretroviral therapy in Malawi. *PLoS medicine*. 2010;7(8).
161. Harries AD, Schouten EJ, Makombe SD, Libamba E, Neufville HN, Some E, et al. Ensuring uninterrupted supplies of antiretroviral drugs in resource-poor settings: an example from Malawi. *Bull World Health Organ*. 2007;85(2):152-5.
162. Johnson LM, K. Kranzer, K. Wood, R. A model of the impact of HIV/AIDS and antiretroviral treatment in the Masiphumelele community. . Cape Town2011. Available from: http://www.publichealth.uct.ac.za/sites/default/files/image_tool/images/108/Masiphumelele%20ART%20model%202011.pdf.
163. National Department of Health South Africa. South African National Antiretroviral Treatment Guidelines. 2004 [cited 2015 07 December]; (First edition.). Available from: http://www.hst.org.za/uploads/files/sa_ART_Guidelines1.pdf.
164. Gutierrez F, Navarro A, Padilla S, Anton R, Masia M, Borrás J, et al. Prediction of neuropsychiatric adverse events associated with long-term efavirenz therapy, using plasma drug level monitoring. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 2005;41(11):1648-53.
165. Dickinson L, Amin J, Else L, Boffito M, Egan D, Owen A, et al. Pharmacokinetic and Pharmacodynamic Comparison of Once-Daily Efavirenz (400 mg vs. 600 mg) in Treatment-Naive HIV-Infected Patients: Results of the ENCORE1 Study. *Clinical pharmacology and therapeutics*. 2015.
166. Holzinger ER, Grady B, Ritchie MD, Ribaldo HJ, Acosta EP, Morse GD, et al. Genome-wide association study of plasma efavirenz pharmacokinetics in AIDS Clinical Trials Group protocols implicates several CYP2B6 variants. *Pharmacogenetics and genomics*. 2012;22(12):858-67.
167. Stahle L, Moberg L, Svensson JO, Sonnerborg A. Efavirenz plasma concentrations in HIV-infected patients: inter- and intraindividual variability and clinical effects. *Therapeutic drug monitoring*. 2004;26(3):267-70.
168. Lehmann DS, Ribaldo HJ, Daar ES, Gulick RM, Haubrich RH, Robbins GK, et al. Genome-wide association study of virologic response with efavirenz-containing or abacavir-containing regimens in AIDS clinical trials group protocols. *Pharmacogenetics and genomics*. 2015;25(2):51-9.
169. Marzolini C, Telenti A, Decosterd LA, Greub G, Biollaz J, Buclin T. Efavirenz plasma levels can predict treatment failure and central nervous system side effects in HIV-1-infected patients. *AIDS (London, England)*. 2001;15(1):71-5.
170. Van Leth F, Kappelhoff, Johnson D, Losso MH, Boron-Kaczmarek A, Saag MS, et al. Pharmacokinetic parameters of nevirapine and efavirenz in relation to antiretroviral efficacy. *AIDS research and human retroviruses*. 2006;22(3):232-9.
171. Dooley KE, Denti P, Martinson N, Cohn S, Mashabela F, Hoffmann J, et al. Pharmacokinetics of efavirenz and treatment of HIV-1 among pregnant women with and without tuberculosis co-infection. *J Infect Dis*. 2015 Jan 15;211(2):197-205.
172. R Core Team. R: A language and environment for statistical computing. Vienna, Austria2015 [cited 2015 01 September]. Available from: <http://www.R-project.org/>

173. Therneau T. A package for survival analysis in S. Version 2.38. 2015 [cited 2015 01 September]. Available from: <http://cran.r-project.org/package=survival>.
174. Therneau TM GP. Modelling Survival Data:Extending the Cox Model. New York: Springer; 2000.
175. Andersen APK GR. Cox ' s Regression Model for Counting Processes : A Large Sample Study. *Ann Stat.* 1982;10(4):1100-20.
176. Klein JP MM. SURVIVAL ANALYSIS, Techniques for Censored and Truncated Data. . Statistics for Biology and Health. New York: Springer-Verlag; 2003.
177. Bienczak A DP, Cook A, Mulenga V, Kityo C, Kekitiinwa A, Owen A, Burger D, Gibb D, Walker S, McIlleron H. The effect of systemic exposure to efavirenz, sex and age on the risk of virological non-suppression in HIV-infected African children. 7th International Workshop on HIV Pediatrics Vancouver, Canada. July 2015.
178. Bangsberg DR, Perry S, Charlebois ED, Clark RA, Roberston M, Zolopa AR, et al. Non-adherence to highly active antiretroviral therapy predicts progression to AIDS. *AIDS (London, England)*. 2001;15(9):1181-3.
179. Bangsberg DR, Hecht FM, Charlebois ED, Zolopa AR, Holodniy M, Sheiner L, et al. Adherence to protease inhibitors, HIV-1 viral load, and development of drug resistance in an indigent population. *AIDS (London, England)*. 2000;14(4):357-66.
180. Orrell C, Dipenaar R, Killa N, Tassie JM, Harries AD, Wood R. Simplifying HIV cohort monitoring--pharmacy stock records minimize resources necessary to determine retention in care. *Journal of acquired immune deficiency syndromes (1999)*. 2013;62(3):e106-8.
181. van Leth F, Phanuphak P, Ruxrungtham K, Baraldi E, Miller S, Gazzard B, et al. Comparison of first-line antiretroviral therapy with regimens including nevirapine, efavirenz, or both drugs, plus stavudine and lamivudine: a randomised open-label trial, the 2NN Study. *Lancet*. 2004;363(9417):1253-63.
182. Puls R, Amin J, Losso M, Phanuphak P, Nwizu C, Orrell C, et al. Efficacy of 400 mg efavirenz versus standard 600 mg dose in HIV-infected, antiretroviral-naïve adults (ENCORE1): a randomised, double-blind, placebo-controlled, non-inferiority trial. *Lancet*. 2014;383(9927):1474-82.
183. van Zyl GU, Claassen M, Engelbrecht S, Laten JD, Cotton MF, Theron GB, et al. Zidovudine with nevirapine for the prevention of HIV mother-to-child transmission reduces nevirapine resistance in mothers from the Western Cape, South Africa. *J Med Virol*. 2008;80(6):942-6.
184. Wensing AM, Calvez V, Gunthard HF, Johnson VA, Paredes R, Pillay D, et al. 2014 Update of the drug resistance mutations in HIV-1. *Topics in antiviral medicine*. 2014;22(3):642-50.
185. Petersen ML, LeDell E, Schwab J, Sarovar V, Gross R, Reynolds N, et al. Super Learner Analysis of Electronic Adherence Data Improves Viral Prediction and May Provide Strategies for Selective HIV RNA Monitoring. *Journal of acquired immune deficiency syndromes (1999)*. 2015;69(1):109-18.
186. Haberer JE, Musinguzi N, Boum Y, 2nd, Siedner MJ, Mocello AR, Hunt PW, et al. Duration of antiretroviral therapy adherence interruption is associated with risk of virologic rebound as determined by real-time adherence monitoring in rural Uganda. [J Acquir Immune Defic Syndr](#). 2015 Dec 1;70(4):386-92
187. Savic RM, Barrail-Tran A, Duval X, Nembot G, Panhard X, Descamps D, et al. Effect of adherence as measured by MEMS, ritonavir boosting, and CYP3A5 genotype on atazanavir pharmacokinetics in treatment-naïve HIV-infected patients. *Clinical pharmacology and therapeutics*. 2012;92(5):575-83.
188. Stone VE, Smith KY. Improving adherence to HAART. *Journal of the National Medical Association*. 2004;96(2 Suppl):27s-9s.
189. Evans D, Menezes C, Mahomed K, Macdonald P, Untiedt S, Levin L, et al. Treatment outcomes of HIV-infected adolescents attending public-sector HIV clinics across Gauteng and Mpumalanga, South Africa. *AIDS research and human retroviruses*. 2013;29(6):892-900.

190. Katz IT KR, Fitzmaurice G, Leone D, Bangsberg DR, Bekker LG, Orrell C. Impact of South Africa's HIV Treatment Guidelines on Early Losses: A Cohort Analysis. Conference on Retroviruses and Opportunistic Infection; 23-26 February.; Seattle.2015.

Appendix 1: TAP study protocol.

The TAP study: Version 2.1, 28 January 2013

A randomised controlled Trial to explore Adherence-failure relationships in a South African antiretroviral delivery site using an electronic adherence device and sparse Pharmacokinetic sampling.

June 2012 to June 2014

Sponsor:

European Drug and Clinical Trial Partnership (EDCTP): TA_11_40200

Host institution:

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1. Study synopsis:

Antiretroviral treatment (ART) options are limited in resource-poor settings, due to large numbers requiring treatment and the cost of supplying it. First-line ART is three times cheaper than second-line ART, is easier to take and is better tolerated, thus maintaining individuals on first line is essential for programme success. Although adherence in adults from resource poor countries is generally reported as excellent, it may be overestimated, as much of this data is generated from tablet return and pharmacy dispensing data. More data is becoming available describing discordance between accepted measured adherence standards and virological failure. In addition, the limited data available on adolescents in resource poor countries on ART, suggests difficulties with adherence. This study will use a locally developed real time electronic adherence monitoring device (EAMD) to explore and improve adherence in individuals commencing new treatment in an established ART cohort in Gugulethu, Cape Town, and use adherence, virological and pharmacokinetic data to examine adherence-failure discordance.

Objectives: To determine whether a real-time electronic adherence monitoring device (EAMD) with text message and dosing feedback improves adherence, retention in care and virological outcomes among individuals receiving new antiretroviral therapy. To determine whether population pharmacokinetic data explain the discordance between adherence and virological response.

Primary endpoint: the proportion of patients with a cumulative adherence by EAMD >95% at week 48 by arm.

Study population and randomisation: Two hundred and twenty ART-naïve HIV-positive patients who are eligible for ART will be recruited from the Hannan Crusaid Treatment Centre, Gugulethu, Cape Town. All will receive an EAMD, then be randomised:

ARM 1 (n=110): Standard of care, using the EAMD to monitor adherence only i.e. without any feedback.

ARM 2 (n=110): Arm one with the addition of the use of the EAMD text message service when dosing late, and EAMD dosing feedback at 4-monthly visits.

Statistical analyses: Data analysis will occur once all patients complete 48 weeks on study. The primary analysis will be an intention-to-treat analysis of any treatment failure with use of Cox proportional hazards regression. Differences in specific reasons for treatment failure (e.g. lost to follow-up, toxicity, death, etc) will be compared by treatment group with hazard ratios and 95% confidence intervals. Differences in time to failure will use Kaplan-Meier analyses. Group comparisons with the log-rank statistic will be regarded as significant if p values are less than 0.05.

Schedule of events: All study visits coincide with visits as per the South African National ART Guidelines, except for the follow-up visit, which is additional.

Visit	Screen	Random- isation	Base- line	Week 16	Week 32	Week 48	Follow- up*
Informed consent	X						
Randomisation		X					
Commence new ART			X				
Dispense EAMD			X				
Adherence review by pharmacy refill and tablet count ^a				X	X	X	
Clinical review ^b	X		X	X	X	X	
Detail adverse events, concomitant medications			X	X	X	X	
Viral load, CD4 count ^{c,d}	X			X		X	
Record dosing time.				X	X	X	
Pharmacokinetic (PK) sampling ^e				X	X	X	
Sample for storage ^f				X	X	X	
CAGE score	X			X		X	
Depression score	x					x	
EAMD acceptability questionnaires				X		X	
Event monitoring and study feedback							X

* The follow-up is the only additional visit required by the study in order to feedback on EAMD adherence assessment. There will be extra samples drawn at standard blood draw times for PK and plasma storage and an additional blood draw for a further PK sample if consent is given.

^a. Adherence review will be done as per standard of care, i.e. through tablet counts.

Feedback from the EAMD device will only be given to those randomised to ARM TWO.

^b. A full clinical examination will be done at screen and month 12, otherwise a symptom-driven targeted examination will be completed.

^c. CD4 counts are completed at baseline and 48 weeks at the HCTC according to the SA National Protocol and viral loads (VL) at week 16 and 48 only. [2] Baseline VL and week 16 CD4 count will require donor funding.

^d If a viral load is >1000 copies at any visit, the test will be repeated within 6 weeks. Two consecutive viral loads > 1000 copies/ml within 6 weeks will constitute virological failure.

^e. Samples for PK will be drawn from all individuals who provide consent. Mid dosing interval levels will be collected for those on efavirenz. Trough levels (C_{min}) will be collected for those on nevirapine, Individuals will act as their own controls. Dosing times will be recorded and confirmed by EAMD. Four ml of blood will be collected per draw in a lithium heparin tube.

^f. Plasma will be stored for all consenting individuals at every on treatment time point for future HIV genotype or pharmacogenetic analysis. (Two x 4ml EDTA tube).

2. Introduction:

2.1 Background.

Increasing numbers of HIV-positive individuals are receiving antiretroviral therapy (ART) in resource limited countries such as South Africa. South Africa has the highest number of people living with HIV (5.7 million), and in the seven years since the introduction of ART 1 058 399 adults and 105 123 children (under age 15) have commenced first-line non-nucleoside reverse transcriptase (NNRTI)-based ART in the public sector alone. [1,2] The numbers of patients failing first-line and commencing second-line ART are increasing with expanded access and time on treatment [3]. Second-line increases the cost of therapy markedly (by at least three times, as of January 2012). First line ART is also easier to take in terms of tablet burden and tolerability. Maintaining people on successful first line therapy is thus a priority.

Adherence as measured by tablet returns and pharmacy refill is excellent in most adult cohorts across sub-Saharan Africa yet despite this failure continues [4-8]. More recently the impact of treatment persistence, examining the impact of duration on therapy and minimising treatment interruptions, on virological outcomes are being explored in these populations. [5,9,10]

Patients taking ART at the Hannan Crusaid Treatment Centre (HCTC), a large public sector antiretroviral roll out site, in Cape Town, South Africa, have been monitored since September 2002. At the end of 2011, 3811 individuals are being treated at the site, with 397 (10%) on second-line therapy. Ten percent of individuals who start first-line ART at the HCTC fail first line therapy by the end of three years. Adherence is monitored at each visit by counting tablet returns. A recent study by this investigator shows adherence is excellent among those who suppress virologically (median 97.8%). It is also excellent for those who fail (median 96.6%). [10] Some of those who fail do so through poor adherence (<80%), but a substantial subset (19%) fail despite adequate adherence [Table 1]. Some of this adherence-failure discordance may be explained by treatment interruptions. Our study also shows that, despite excellent adherence (>95%) when in possession of ART, a single treatment interruption increases the odds of failure by 5.65 (CI 1.40-22.85). [10] Overestimation of adherence may also be an explanatory factor when using tablet counts as a measure. In another study by our group exploring different adherence measures in the paediatric cohort of the HCTC, tablet/syrup returns overestimated adherence by 8% compared to MEMScaps data. [11] Poor timing of the twice daily doses was also noted in this study. Other factors that have not been thoroughly explored may also impact, such as drug bioavailability, which may differ in our population. It is already known that efavirenz metabolism differs in a sub-Saharan African population, due to genetic variants in the cytochrome p450 2B6 enzyme. [12]

Table 1: proportion of patients with concordant or discordant adherence-virological outcomes at 48 weeks (n=211).

At week 48 on first-line ART*	Viral load ≤50 copies/ml	Viral load >50 copies/ml
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Cumulative adherence \geq 95%	Expected viral suppression n=124 (59%)	<i>Unexpected non-suppression</i> n=41 (19%)
Cumulative adherence <95%	<i>Unexpected viral suppression</i> n=28 (13%)	Expected non-suppression n=18 (7%)

*Tablet count adherence data from HCTC cohort as described by Ncaca, Kranzer and Orrell. [13]

Limited research has been conducted to determine virologic, immunologic and mortality outcomes in adolescents on ART in South Africa, and findings indicate significantly lower virological suppression and increased virological failure in adolescents compared to young adults in a peri-urban setting in Cape Town, the Hannan Crusaid Treatment Centre and the authors suggest poor adherence as a possible explanation for their finding.[14] A further study measuring both virological outcomes and adherence in adolescents compared to adults in a private sector disease management program in 9 countries in Southern Africa, (including South Africa), found significantly poorer adherence in adolescents compared to adults and a significant relationship between adherence and virological suppression.[15]

The majority who fail first-line ART in resource poor settings have at least dual class resistance at first-line failure, usually including resistance to lamivudine and the chosen NNRTI, either efavirenz or nevirapine. [13,16,17] Much of this resistance is likely to occur due to prolonged time spent on the failing ART regimen where viral loads are a limited resource, due to their cost. In a cohort where viral load monitoring was more tightly monitored, these resistance patterns were similar though much less frequent and complex. [18] We have shown that an intensive adherence intervention results in 67% of those who have a first viral load >1000 copies/ml being re-suppressed at the subsequent viral load. [3, 19] Tight control of adherence with early intervention thus is likely to reduce the time that virus is exposed to sub-therapeutic drug levels.

The 2010 South African ART guidelines have reduced the number of viral loads available for the ART programme. Two are allowed in the first year (one at 4 months, the other at 12 months) and thereafter a single viral load is permitted annually. [2] With such sparse monitoring there is a great need for an affordable, real time adherence-monitoring device that is acceptable to the ART-taking population. Use of such a device would allow exploration of adherence-failure-resistance relationships in more detail and allow real-time monitoring of adherence in those deemed to require such an intervention.

2.2 Study hypotheses and goals:

This study will explore the acceptability and impact of a locally produced, novel, wireless, electronic adherence monitoring device (EAMD), on adherence behaviour in ART-naïve individuals commencing ART at the HCTC. Other studies using a similar device have been completed in Kenya and Uganda. [20,21] We hypothesise that the use of real-time monitoring will reduce the overestimation of adherence seen with current methods. With the addition of a reminder sent by text message in the randomised arm should dosing be late, we hypothesise that the electronic adherence monitoring device will improve adherence, reduce treatment interruptions and subsequently reduce first-line ART failure rate (two consecutive viral loads >1000 copies/ml). In 2007, up to 92% of South Africans carried cell phones, so the use of reminder text messages should be feasible in our population [<http://www.gapminder.org/>]. Pharmacokinetic samples will be collected from

all individuals who give consent. If on efavirenz, two mid-dosing interval time points will be drawn an hour or more apart at each visit (this will allow description of elimination and an estimate the trough concentration). For those on nevirapine or lopinavir/r, a predose trough will be drawn. These samples allow for sparse population pharmacokinetic (PK) analysis as well as exploration of PK results in those with discordant adherence-failure outcomes i.e. those with good adherence (>95%) and viraemia (>50 copies RNA/mL) or poor adherence (<95%) and virological suppression. We will also qualitatively investigate the reasons for poor adherence e.g. personal life events, alcohol use (shown to impact on early poor adherence [Daniella Mark – personal communication]), disclosure of HIV status, evidence of depression or anxiety or poor tolerance of medication, as well as the relationship between complex adherence patterns and viral failure, in order to lay the foundation for an adherence intervention that might prevent viral failure after missed doses, but before viral rebound. Data will be available for cost-effectiveness analyses.

Adherence research with this depth has not been completed before. In addition to the impact of an electronic adherence monitoring device (EAMD) on adherence, retention in care and virological outcomes, we will examine detailed pharmacokinetic results in the same cohort, while storing specimens for future pharmacogenetic and HIV genotyping studies.

This study is entirely in line with the Desmond Tutu HIV Centre's goals and strategies to impact policy and practice both nationally and internationally through research relevant to a country that remains the epicentre of HIV and TB epidemics; as well as in line with that of the host institution, UCT, to "address the health challenges facing South African and African society" by "undertaking research relevant to Africa's needs."
[<http://www.health.uct.ac.za/about/mission/>]

2.3 Principal research questions

1. Does a real-time electronic adherence monitoring device (EAMD) with text message feedback improve adherence, retention in care and virological outcomes among ART-naïve individuals receiving new antiretroviral therapy?
2. Does population pharmacokinetic data explain discordance between adherence and virological response?

3. Study design and endpoints:

3.1 Study methodology.

A randomised study over 48 weeks investigating the impact of a real-time electronic adherence monitoring device on adherence and persistence to ART therapy of ART-naïve individuals on first-line ART. All individuals who consent to additional sampling will be enrolled in a voluntary pharmacokinetic substudy.

3.2 Study design.

The study is described in Table 2. ART-naïve participants at the HCTC will commence their new treatment as per the clinic routine, with the addition of study information at one treatment preparedness session and an informed consent process.

Inclusion criteria:

- ART-naïve individual (< 1 month prior ART) 12 years or older. Women who have completed pMTCT will be considered naïve.
- Been prescribed new antiretroviral therapy by a Hannon clinician.
- At least one medication of the regimen must be in tablet formulation.
- Willing to sign the patient informed consent if 18 years of age or above, or assent if 17 years old or below, to participate in the study. Parent or legal guardian must be willing to provide written consent for their child to participate in the study if 17 years or below.

Exclusion criteria:

- Active disease which, in the opinion of the study staff, would preclude the informed consent process.
- Participant or carer not in possession of a cellular telephone.

A log of those who do not meet inclusion/exclusion criteria will be kept.

The EAMD will be dispensed at time of ART initiation. The chosen EAMD (Wisepill®) is a locally-produced, affordable electronic device the size of a mobile phone which can store up to a week of medication either as a blister pack or a seven compartment pill box (figure 1). On opening, a signal is sent via the mobile-phone network to a central computer, thus recording adherence behaviour in real time. There is an option to send a reminder by text message to the participant's mobile phone.

Table 2: study schematic.

Screen (week -4 to 0)	Week 0.	Weeks 16, 32 and 48 – randomised phase. All receive standard of care at the HCTC with the addition of the ARM 1 or 2 details.
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Informed consent process. All receive standard of care treatment preparedness at HCTC.	Randomise (dispense Wisepill® device)	ARM 1(n=110): Use of EAMD without text message feedback. Visits occur according to standard of care at HCTC.
		ARM 2 (n=110): Use of EAMD with text message service when dosing late. Report of adherence behaviour given at each 4-monthly visit. Visits occur according to standard of care at HCTC.

Figure 1: The electronic adherence monitoring device (Wisepill®).



3.3 Randomisation.

A minimum of 220 people will be randomised 1:1 (110:110) to one of the two treatment arms:

ARM 1(n=110): Standard of care, using the EAMD to monitor adherence only i.e. without any feedback.

ARM 2 (n=110): Arm one with the addition of the use of the EAMD text message service when dosing late, and EAMD dosing feedback at 4-monthly visits.

3.4 Study visits.

Screening visit: All patients at the study site are seen by a (non-study) clinician on first attendance. Demographic details are recorded at this visit, with WHO clinical staging. Blood will be drawn for baseline viral load after the informed consent process is complete. CD4 count data will be extracted from the Hannan patient file. Screen questionnaires (CAGE, disclosure status and Hospital Anxiety and Depression Scale) will be completed. This data is transferred into the HCTC Access database on a weekly basis and will be collected for the purposes of this study directly from the data base.

All potential ART patients return for 3 treatment-preparedness sessions managed by the counselling team. At the first visit, in addition to the treatment readiness session, a study counsellor will describe the study and invite patients to participate. If they agree to participate, they will be given an appointment to meet the investigator or study coordinator for a full informed consent process. The informed consent document is attached as

Appendix 1. If consent is given, each individual will be randomised on a 1:1 basis to ARM 1 (EAMD with reminder) or ARM 2 (EAMD no reminder) prior to their planned ART start date.

Week 0 (ART start date): At this visit the SCO will explain the use of the EAMD with or without details of reminders as per randomised arm. If randomised to reminders (ARM 1) the SCO will establish planned times of dosing and preferred time lag prior to reminder being sent. ART will be started by the HCTC (non-study) clinician as per standard practice. Details of the treatment regimen will be captured through the HCTC Access database. Baseline questionnaires on disclosure status, alcohol use and the Hospital Anxiety and Depression score (HADS) will be completed.

Should the inclusion and exclusion criteria be met, then screen and week 0 may be completed on the same day.

Weeks 16, 32 and 48 (on treatment visits): The participants will complete standard HCTC visits by non-study clinical and phlebotomy staff. Adherence will be monitored and responded to based on tablet count data and a clinical visit will be completed. For individuals on ARM 2, feedback from the EAMD data will be placed in their patient files for the clinicians to review at these visits. Cell phone numbers will be confirmed at every visit. Visit windows will stretch from 8 weeks before the scheduled date to 8 weeks after the scheduled date.

Blood for CD4 cell count, viral load, first PK sample and plasma for storage will be drawn at weeks 16 and 48. At week 32, only blood for PK and plasma storage will be drawn. Time of blood draw will be recorded as will time of most recent ART dosing. A sample of hair for PK analysis will be taken should the patient permit.

Should patients need additional counselling the study counsellors will be available to provide this. EAMD acceptability and the CAGE questionnaire will be completed by the study counsellors at weeks 16 and 48. The HADS will be completed again at week 48.

Pharmacokinetic data: The study coordinator will complete the blood draw at each study visit. Blood will be taken for PK and for storage as per table 3 (schedule of events).

Follow-up visit: At this visit, one month after week 48, all participants will be given feedback from their EAMD data. A questionnaire describing life events perceived to impact on adherence over the 48 weeks will be administered.

Drug dispensing: Dispensing will be as per standard of care. Patients will be given one month of medication (in four patient-ready weekly EAMD pillboxes) per month for the first four months and resupplied two-monthly (with eight patient-ready weekly EAMD pillboxes) for the rest of the study.

3.5 Study duration.

Each individual would be followed until 52 weeks after start of new ART (48 weeks on study, with a follow-up visit 4 weeks later). Further care will be continued at the HCTC as per standard of care.

3.6 Primary outcome.

Primary outcome: proportion of patients with a cumulative adherence by EAMD >95% at week 48 by arm.

3.7 Secondary outcomes.

1. Virological outcome: Proportion of patients with a viral load of <50 copies/ml at week 48; as well as proportion of patients who failed (consecutive VL >1000 copies/ml) by week 48.
2. Adherence: comparison of cumulative EAMD adherence data and tablet count adherence data at weeks 16, 32 and 48.
3. Retention in care: proportion of patients still in care at 48 weeks (excluding those transferred to other ART sites); proportion with a treatment interruption of >72 hours.
4. Pharmacokinetic: Mid-dosing efavirenz levels or trough nevirapine and lopinavir levels for discordant participants at weeks 16, 32 and 48.
5. Exploratory endpoint: relationship of PK results to adherence and to virological outcome at week 16, 32 and 48.
6. Qualitative endpoints: Acceptability of EAMD device; impact of qualitative issues on adherence (alcohol, disclosure, mental health status, ART tolerability, life events).

3.8 Withdrawal of participants from the study.

Participants will be withdrawn from the study only if they withdraw consent.

Death and loss to follow-up will be recorded and analysed as part of the retention in care secondary outcome.

Transfer out: a patient transferred to another clinic will be considered still in care.

Patients who fail virologically will have reached an endpoint but will remain on the study with their new regimen.

3.9 Standard of care at the Hannan Crusaid Treatment Centre.

Care at the HCTC is provided according to the South African National ART Guidelines of 2010. [2] Patients who meet the criteria for ART initiation (CD4<350cells/ml, WHO stage 4 disease) usually initiate ART four weeks after their first/screening visit. In those four weeks they are encouraged to attend 3 group treatment preparedness sessions and will have pre-treatment safety bloods drawn as part of their clinical assessment.

Preferred first-line ART includes tenofovir (TDF), 3TC and either efavirenz or nevirapine. Efavirenz is the non-nucleoside reverse transcriptase inhibitor (NNRTI) of choice, and only women who plan to conceive in the next few years will be offered nevirapine. Should tenofovir be inappropriate (age or renal insufficiency), then zidovudine (AZT) can be prescribed instead.

Patients are seen monthly for the first four months, and after that they attend every second-month. Two months of medication is given at one time after month four. Viral loads are assessed at 4 months into treatment, at a year into treatment and then annually. Once a patient has a second viral load <50 copies/ml (usually at a year into ART) then they may be transferred to an adherence club or the green clinic where they have fewer visits and annual clinical assessments.

Failure is defined at two consecutive viral loads >1000 copies/ml, after which second-line ART is offered.

4. Statistical methodology:

4.1 Study site and population.

The study will be conducted at the Hannan Crusaid Treatment Centre (HCTC) in Gugulethu, Cape Town. The HCTC is one of four public-sector antiretroviral delivery sites in the Klipfontein Health Sub-district of Cape Town. The clinic, which commenced delivery of ART in September 2002, is currently treating 3811 people. An average of 75 people commenced first-line ART every month over the last calendar year to 31 December 2011.

The site is staffed by 7 clinicians (4 medical officers and 3 clinical nurse practitioners), a pharmacist and 30 therapeutic counsellors who provide treatment preparedness education (in the form of three group sessions), and on-treatment adherence support, including intensive individual adherence sessions as indicated by poor tablet returns or raised viral load (>50 copies/ml). CD4 cell counts are completed at baseline and month 4, then at month 12 and annually thereafter. Viral load monitoring is completed at 4 months, 12 months and annually thereafter. [2] All demographic, clinical and laboratory data are recorded in an off-site Access database and validated annually.

4.2 Human participants.

All ART-naïve individuals enrolling on new ART at the HCTC (adults and adolescents) will be invited to enrol in the study, until the study numbers have been achieved. Subjects will be informed about the study at one of the group education sessions and invited to approach the study counsellor at one of the scheduled visits during the 4 week pre-treatment ART-preparedness period. Individual informed consent and/or assent will be signed with one of the study staff during a scheduled clinic visit before randomisation and commencing ART.

4.3 Sample.

Patients at the HCTC are representative of the typical South African population receiving ART, with a predominance of women accessing the service (67%) and a median CD4 of 104 cells/mm³ at initiation of first line therapy. [22] Approximately 75 ART-naïve individuals commence treatment each month at the HCTC and all individuals attending the clinic for new ART will be approached to join the study over the recruitment period. Recruiting a sample size of 220, assuming 90% agree to join the study, should take 4 to 5 months.

4.4 Sample size determination:

An estimated 200 people will need to be randomised on a 1:1 basis to have >90% power to detect a 10% difference in virological suppression to a significance of 0.05. We intend to recruit 230 to account for loss of 10% of the population due to death or loss-to-follow up in the first year of therapy, [19] and an additional 10 people to account for transfers out to other clinics.

4.5 Analysis including statistical methods:

Baseline differences in randomisation groups will be described with simple proportions for categorical variables and means (+/- standard deviations) or median (+/- inter quartile

range) for numerical variables. The primary analysis will be an intention-to-treat analysis of any treatment failure with use of Cox proportional hazards regression. Differences in specific reasons for treatment failure (e.g. lost to follow-up, toxicity, death, etc) will be compared by treatment group with hazard ratios and 95% confidence intervals. Differences in time to failure will use Kaplan-Meier analyses. Group comparisons with the log-rank statistic will be regarded as significant if p values are less than 0.05.

Data analysis will occur once all patients complete 48 weeks on study.

5. Study conduct:

5.1 Ethics:

The site has ethical approval for the ongoing collection of routine clinical and laboratory data. All patients at the HCTC have signed individual informed consent and/or assent to this end. This study will require additional informed consent to incorporate the use of the EAMD device and additional data collection including questionnaires. There will also be additional blood draws. The committee may enquire into the ethics of not using the EAMD feed back messages available in arm 1 as study staff may be able to identify participants with poor adherence while on study. We would argue that the study should not impact standard of care and clinic staff should identify those most at risk through tablet counts, as is currently the case.

This study will also be submitted to the Western Cape Provincial Department of Health research committee for approval.

5.2 Justification of use of questionnaires.

We intend to avoid loading this cohort with questionnaires as we would prefer the EAMD to be the key intervention, rather than the presence and impact of the researchers. As such the data collected by questionnaire will be kept to a minimum. Alcohol, disclosure status, depression and anxiety all have reported impact on adherence to ART and this data will be collected at baseline. The CAGE questionnaire (appendix 2) is the simplest effective questionnaire to identify individuals with alcohol use issues and is a tool already available to clinic staff. Disclosure will be examined by two simple questions: "Have you disclosed your HIV status to anyone?" If yes, "to whom?" Mental health status will be assessed through the hospital anxiety and depression scale (HADS) which contains only 14 items and has been validated for adults and adolescents (appendix 3).

Adverse event data is not routinely captured at this clinic, but will be collected for study purposes by asking a single open question ("Have you noted any problems you relate to use of your medication?") and explored as necessary.

A short questionnaire will be formulated to elicit acceptability of the EAMD device. Stigma related to HIV is still widespread in South African communities so the device needs to be discreet and the text messages subtle. At the end of the study adherence data from the EAMD device will be given to each participant and significant changes in pattern explored. Details of this questionnaire will be presented in a subsequent protocol.

5.3 Patient informed consent.

The patients will undergo an informed consent process as per the DTHC standard operating procedure (SOP). In short, the study may be explained in a group setting, in the patient's home language, and the patient given a copy of the ICF to read. There will be ample time allowed for questions. The ICF will be signed with the study staff in an individual consultation with privacy for further questions thereafter. Those under 18 years will not be able to participate without both their assent and their parent/legal guardian's consent.

5.4 Patient confidentiality.

Data: No data containing patient identifiers (name or address) will leave the HCTC site.

Staff: All DTHC staff sign a confidentiality statement on commencing employment with the Centre. They are made aware of the sensitivity of patient information and any breach of confidentiality is treated with the utmost severity.

5.5 Patient compensation.

Patients on this study will continue to receive ART as standard of care at their community clinic. They will receive R20 in financial compensation for being the extra time spent at the clinic due to completing the questionnaires and the extra blood which is drawn during the study. This compensation will be given at each of the 5 study scheduled visits only. These coincide with the scheduled ART visits. The patient will be reimbursed R150 for the final or post-study visit, which is an additional visit.

6. Study procedures and observations:

The items listed in table 3 below will occur at the specified study visit. Antiretroviral therapy will be decided as per the HCTC standard of care, and clinical visits will also occur as per their protocol and are not considered study procedures. Adverse events and laboratory safety blood results will be managed as per standard of care by HCTC clinicians and are not study procedures, although adverse events will be recorded e.g. concomitant use of rifampicin for treatment of tuberculosis, due to their potential impact on ART dosing or drug levels.

Table 3: Schedule of events:

Visit	Screen	Random- isation	Base- line	Week 16	Week 32	Week 48	Follow- up*
Informed consent	X						
Randomisation		X					
Commence new ART			X				
Dispense EAMD device			X				
Adherence review by pharmacy refill and tablet count ^a				X	X	X	
Clinical review ^b	X		X	X	X	X	
Detail adverse events, concomitant medications			X	X	X	X	
CD4 count ^c	X			X		X	
Viral load ^{c,d}	X			X		X	
Record dosing time.				X	X	X	
Pharmacokinetic (PK) sampling – serum and hair ^e				X	X	X	
Sample for storage ^f				X	X	X	
Disclosure status	X		X	X	X	X	
HADS	X					X	
CAGE	X			X		X	
EAMD acceptability questionnaires				X		X	
Event monitoring and study feedback							X

* The follow-up is the only additional visit required by the study in order to feedback on EAMD adherence assessment. There will be extra samples drawn at standard blood draw times for PK and plasma storage. ^a. Adherence review will be done as per standard of care, i.e. through tablet counts. In ARM 2 a report of adherence from the EAMD will be given to the clinician for discussion. No feedback from the EAMD device will be given until the follow-up visit (week 52) for those in ARM 1.

^b. Clinical procedures will occur as per standard of care at the HCTC.

^c. CD4 counts are completed at baseline 48 weeks at the HCTC according to the SA National Protocol [2]. Viral loads (VL) are only completed at weeks 16 and 48 at the HCTC according to the SA National Protocol [2]. Baseline viral loads and week 16 CD4 counts will be added through donor funding for this study.

^d If a viral load is >1000 copies at any visit another will be repeated within 6 weeks. Two consecutive viral loads > 1000 copies/ml constitutes virological failure. Patients will remain on study despite reaching an endpoint.

^e. Samples for PK will be drawn from all individuals who provide consent. Mid dosing interval levels will be collected for those on efavirenz and trough levels (C_{min}) for those on nevirapine or lopinavir/r. Individuals will act as their own controls. Four millilitres of blood will be collected per draw in a lithium heparin tube.

Dosing times will be recorded and confirmed by EAMD. Hair samples (head or axillary) will also be collected.

^f. Plasma will be stored for all consenting individuals at every “on treatment” time point for future HIV genotype or pharmacogenetic analysis (2 x 4ml EDTA tubes). Plasma aliquots from EDTA tubes will be kept at -70°C until analysis.

7. Reports and study output:

7.1. Plan for dissemination of study results.

Outcomes from this study would include at least two peer-reviewed publications (one describing the primary outcome and another the pharmacokinetic data) as well as motivations to the Provincial Department of Health for continued use of the EAMD device should it prove to be beneficial in adherence and retention in care. Information on adherence patterns and PK issues leading to discordance will be incorporate into clinical practice through in-service training at local meetings. Should this not have the benefit we expect, we will incorporate all we learn about adherence behaviour into pre-and on-treatment education sessions and if necessary design a new intervention to make best use of the results. Many clinical practice improvements from the HCTC have been incorporated into the Western Cape and South African Antiretroviral guidelines in the past 7 years.

7.2. Project plan with timescale and milestones.

Figure 1: Overall trial timeline.

Time from funding approval (in months):	0-3	4-6	7-9	10-12	13-15	16-18	19-21	22-24	25-27	28-30
Protocol completion										
Ethics submission										
Staff training										
Participant recruitment*										
Study follow-up.										
Data analysis										
Report writing.										

* Funding approval was received on 29 February 2012, so this project aims to be completed by September 2014.

8. Study administration:

8.1. Project management.

The study coordinator on site at the Hannan Crusaid Treatment Centre will manage the project on a day-to-day basis. Three counsellors will be assigned to the project and will assist in managing bookings and completing questionnaires. Participants will be seen by staff of the HCTC as per standard of care and will follow the standard routine for treatment preparedness and on-treatment visits. HCTC counsellors routinely manage the 3 treatment preparedness sessions and count tablet returns at each visit. Both clinical nurse practitioner and doctors are available for clinical review. Standard blood draws will be drawn by the HCTC phlebotomy staff. The extra blood draw required for the PK samples will be completed by the study coordinator. Clinical, laboratory and adherence details necessary will be collected by the study coordinator after the visits and from the HCTC access database.

8.2. Study staff roles.

The investigator (Dr. Catherine Orrell): The investigator is responsible for the overall running of the study, including protocol development; staff and patient recruitment; ethics submissions; the informed consent process; maintaining study integrity; collection of data; data analysis and dissemination of results.

Study coordinator: The SCO manages the study on a day to day basis; maintains and manages the booking diary; manages the counsellors on-site; identifies study participants in the clinic; identifies missing participants; completes the case report forms; draws the extra blood samples and prepares them for storage.

Counsellors: The Sizophila counsellors are an established group of HIV-positive lay staff who are educated to support others living with HIV on ART. The HCTC employs 30 counsellors. This study will support five of these well-trained counsellors who will be seconded to the study for the duration of the work counsellors (one of whom will have received adolescent sensitivity training). These counsellors will provide pre and on-treatment counselling including treatment preparedness and additional adherence counselling; provide EAMD education; complete tablet counts at each visit; administer study questionnaires at each visit; do home visits as per standard protocols; and assist the SCO in managing patient bookings and visits.

Data manager and statistician: Dr Carl Morrow (PhD) is an experienced data manager and has maintained DTHC research databases for three and a half years. He is skilled at extracting and analyzing relevant information that is translatable into published products. His expertise in working with, maintenance and development of the Gugulethu ARV database will provide support and insight into the data collection and subsequent analysis for this project. His experience in statistics gained during his PHD work will allow for rigorous analysis of the data from this project. He will be responsible for data management including data collation and entry, cleaning of the data and subsequent data analysis.

Quality Management: Christie Heiberg is a qualified clinical trials monitor. The role of the quality manager is to ensure that adequate approvals are in place for the study to be

conducted; ensure that all subjects have signed an informed consent form; to monitor a random sample of subjects to ensure adherence to the protocol; to identify protocol deviations, report them accordingly, identify and implement corrective action to ensure that errors are not repeated; to ensure that all safety reporting is done according to the protocol and ethics committee requirements; to ensure that the principal investigator is provided with written and verbal feedback after each monitoring visit and, at the end of the study, ensure that all the documentation is in place and that the study is ready for archiving.

9. References:

1. Statistics South Africa Mid-year Population Estimates 2011. (Updated 27 July 2011, accessed 18 January 2012). Available from <http://www.statssa.gov.za/publications/statsdownload.asp?PPN=P0302&SCH=4986>
2. National Department of Health SA. Clinical Guidelines For The Management Of HIV & AIDS In Adults And Adolescents. 2010. (updated April 2010, accessed June 6, 2010). Available from <http://www.doh.gov.za/docs/>
3. Orrell C, Harling G, Lawn SD, Kaplan R, McNally M, Bekker L-G, Wood R. Conservation of first line antiretroviral treatment regimen where therapeutic options are limited. *Antiviral Therapy* 2007; 12: 83-88.
4. Orrell C, Bangsberg D, Badri M, Wood R. Adherence is not a barrier to successful antiretroviral therapy in South Africa. *AIDS* 17:1369-1375, 2003.
5. Bae JW, Guyer W, Grimm K, Altice FL. Medication persistence in the treatment of HIV infection: a review of the literature and implications for future clinical care and research. *AIDS*. 2011 Jan 28;25(3):279-90.
6. Mills EJ, Nachega JB, Buchan I, Orbinski J, Attaran A, Singh S, Rachlis B, Wu P, Cooper C, Thabane L, Wilson K, Guyatt GH, Bangsberg DR. Adherence to antiretroviral therapy in sub-Saharan Africa and North America: a meta-analysis. *JAMA*. 2006 Aug 9;296(6):679-90. Review.
7. Bisson GP, Rowh A, Weinstein R, Gaolathe T, Frank I, Gross R. Antiretroviral failure despite high levels of adherence: discordant adherence-response relationship in Botswana. *J Acquir Immune Defic Syndr*. 2008 Sep 1;49(1):107-10.
8. Nachega JB, Marconi VC, van Zyl GU, Gardner EM, Preiser W, Hong SY, Mills EJ, Gross R. HIV Treatment Adherence, Drug Resistance, Virologic Failure: Evolving Concepts. *Infect Disord Drug Targets*. 2011 Apr 1;11(2):167-74.
9. Kranzer K, Lewis JJ, Ford N, Zeinecker J, Orrell C, Lawn SD, Bekker LG, Wood R. Treatment interruption in a primary care antiretroviral therapy program in South Africa: cohort analysis of trends and risk factors. *J Acquir Immune Defic Syndr*. 2010 Nov 1;55(3):e17-23.
10. Ncaca L-N, Kranzer K, Orrell C. Treatment interruption & variation in tablet taking behaviour result in viral failure: a case-control study from Cape Town, South Africa. *PLoS One*; 6(8):e23088. Epub 2011 Aug 8.
11. Müller AD, Jaspan HB, Myer L, Hunter AL, Harling G, Bekker LG, Orrell C. Standard measures are inadequate to monitor pediatric adherence in a resource-limited setting. *AIDS Behav*. 2011 Feb;15(2):422.
12. Cohen K, Grant A, Dandara C, McIlleron H, Pemba L, Fielding K, Charalombous S, Churchyard G, Smith P, Maartens G. Effect of rifampicin-based antitubercular therapy and the cytochrome P450 2B6 516G>T polymorphism on efavirenz concentrations in adults in South Africa. *Antivir Ther*. 2009;14(5):687.
13. Orrell C, Walensky RP, Losina E, Pitt J, Freedberg KA, Wood R. HIV-1 clade C resistance genotypes in naïve patients and after first virological failure in a large community ART programme. *Antiviral Therapy* 2009; 14(4):523-31.
14. Nglazi, M.D., Kranzer, K., Holele, P., Kaplan, R., Mark, D., Jaspan, H., Lawn, S.D., Wood, R., and Bekker, L-G. (in press). Treatment outcome in HIV-infected adolescents attending a community-based antiretroviral clinic in South Africa. *BMC Infectious Diseases*, 12, 21
15. Nachega, J.B., Hislop, M., Nguyen, H., Dowdy, D.W., Chaisson, R.E., Regensberg, L., Cotton, M., and Maartens, G. (2009). Antiretroviral therapy adherence, virologic and

immunological outcomes in adolescents compared with adults in Southern Africa. *JAIDS*, 51 (1), 65-71

16. Wallis CL, Mellors JW, Venter WD, Sanne I, Stevens W. Varied patterns of HIV-1 drug resistance on failing first-line antiretroviral therapy in South Africa. *J Acquir Immune Defic Syndr*. 2010 Apr 1;53(4):480-4.

17. Hosseinipour MC, van Oosterhout JJ, Weigel R, Phiri S, Kamwendo D, Parkin N, Fiscus SA, Nelson JA, Eron JJ, Kumwenda J. The public health approach to identify antiretroviral therapy failure: high-level nucleoside reverse transcriptase inhibitor resistance among Malawians failing first-line antiretroviral therapy. *AIDS*. 2009 Jun 1;23(9):1127-34.

18. Wallis C, Papathanasopoulos MA, Fox M, Conradie F, Ive P, Orrell C, Zeinecker J, Sanne I, Wood R, McIntyre J, Stevens W on behalf of the CIPRA-SA project 1 study team. Low rates of complex resistance detected in a well monitored cohort in South Africa (CIPRA-SA). *Antiviral Therapy*, in press. 2011.

19. Orrell C, Kaplan R, Wood R and Bekker LG. Virological Breakthrough: A Risk Factor for Loss to Follow-up in a Large Community-Based Cohort on Antiretroviral Therapy. *AIDS Research and Treatment*, vol. 2011, Article ID 469127, 2011.

20. Pop-Eleches C, Thirumurthy H, Habyarimana JP, Zivin JG, Goldstein MP, de Walque D, MacKeen L, Haberer J, Kimaiyo S, Sidle J, Ngare D, Bangsberg DR. Mobile phone technologies improve adherence to antiretroviral treatment in a resource-limited setting: a randomized controlled trial of text message reminders. *AIDS*. 2011 Mar 27;25(6):825-34.

21. Haberer JE, Kahane J, Kigozi I, Emenyonu N, Hunt P, Martin J, Bangsberg DR. Real-time adherence monitoring for HIV antiretroviral therapy. *AIDS Behav*. 2010 Dec;14(6):1340-6.

22. Nglazi MD, Lawn SD, Kaplan R, Kranzer K, Orrell C, Wood R, Bekker LG. Changes in programmatic outcomes during 7 years of scale-up at a community-based antiretroviral treatment service in South Africa. *J Acquir Immune Defic Syndr*. 2011 Jan 1;56(1):e1-8.

Appendix 1: Adult informed consent



Adult information leaflet and consent form for the TAP study.

A randomised controlled Trial to explore Adherence-failure relationships in a South African antiretroviral delivery site, using an electronic adherence device and sparse Pharmacokinetic sampling.

Introduction: You have been asked to read this information as you are HIV-positive and about to commence new antiretroviral treatment (ART) at the Hannan Crusaid Treatment Centre (Hannan) in Gugulethu, Cape Town. You also have a cell phone.

When you start ART you will be taking a number of tablets every day. In order for the ART to keep working for you for the rest of your life, you have to take this medication at the same time every day, as prescribed. Usually we check how well you are doing by seeing that you come regularly to the clinic and by counting the tablets that you bring back. At the moment there are thousands of people receiving ART from this clinic and it is becoming harder for the staff to make sure that everyone is doing well on their treatment all the time.

Purpose of the study: We would like to ask you to be part of a research study that will help us to answer two research questions. 1. Will reminding people to take their ART every day by SMS help them to take their ART better than those who are not reminded? 2. What do the levels of ART in the blood look like in these groups of people?

The TAP study details and duration: If you agree to be on the study, you will be given a small electronic pill box called the Wisepill when you start your ART. This device can fit in your pocket, and helps to monitor when you take your tablets. There is picture of this pill box below:



You would receive your treatment in plastic pillboxes (one per week) which slide into the Wisepill device as shown in the picture. You would open the device when you need to take your medication and take out the tablets you need. When you open and close the lid of this box, it sends a signal to a computer here at Hannan to let us know when you have taken your tablets.

In total there will be 220 people on the study, all from Hannan. Those who agree to join this study will be given this pill box and taught how to refill it every week. There will be two arms to this study and you would be assigned to one of the arms randomly (like flipping a coin).

In arm 1: you would continue to receive the same care at Hannan as everyone else, with the addition of using the electronic pill box.

In arm 2: in addition to receiving usual care at Hannan and using the pill box, you would also get a reminder by SMS on your cell phone if you do not take your tablets within an hour of your usual dosing time. You would also be given a report showing when you took your tablets at your 4-monthly clinical visit.

The study will continue for a year from your ART start date.

Being on this study is your own decision (voluntary). You may choose NOT to participate in this study and you will then continue to receive good care at Hannan without any problems.

Study procedures: At your clinic visits, in addition to the usual procedures we will ask you some questions about how easy or hard it is for you to use the pill box and a few short questions about whether you use any alcohol, have disclosed your HIV status to anyone or are feeling depressed or anxious. At the end of the study we will ask you if you can think of anything happening in your life over the time of the study that may have changed the way you took your ART.

We will collect some information about you such as your age, gender, stage of HIV disease and assigned treatment. All this information will be kept completely confidential and accessed only by study staff using your clinic number e.g. XX 9876 and not your name.

At most of the visits we will need to take extra tubes of blood. Before the study starts we would like to count the HIV in your blood (viral load) as well as look at the CD4 count that is usually taken. At each of the three visits we would like two or three extra tubes of blood

















(10-15ml or 2-3 teaspoons) to study the levels of the ART in your blood and to store for later resistance testing, if needed. We would also like to collect a few strands of your hair (from your head / arm pit) at each visit, if you agree.

There should be no reason for you to need extra clinic visits due to the use of the pill box or being on the study. Each time you come to the clinic we will replace the battery on the pill box (a battery lasts about 4 months).

The study is voluntary: This means you can choose not to join the study or you can leave the study at any time without this causing a problem with you receiving ART at Hannan.

Withdrawal from the study: You can withdraw from this study at any time without impacting your ART at Hannan. You may be withdrawn from the study by the study team only if the sponsor terminates the study.

The table below describes what will happen at each visit during the TAP study (these are procedures that will happen in addition to your normal visit at Hannan).

Screen visit	Base-line	Week 16	Week 32	Week 48	Follow-up
Sign informed consent 	Given EAMD with explanation. 				Review of EAMD results 
Blood taken for viral load (5ml)&. 		Blood taken for CD4 (5ml) drug levels (5ml) and to store for genotype (10ml)*  	Blood taken for drug levels (5ml) and to store for genotype (10ml)  	Blood taken for drug levels (5ml) and to store for genotype (10ml) §  	
Disclosure, CAGE and depression questionnaire  e		Disclosure, and CAGE questionnaire  e		Disclosure, CAGE and depression questionnaire  e	
		EAMD acceptability questionnaire  e		EAMD acceptability questionnaire  e	Life events questionnaire  e

& In additional to CD4 count drawn at this visit

* In addition the viral load drawn at this visit.

§ In addition to the CD4 and viral load drawn at this visit.

Please remember to come to the clinic before taking your morning dose of ART (if you have one)

Participant responsibilities: You will be expected to take care of the device you are given and to make sure the battery is charged (either by charging it at home or coming to the clinic for a new battery) . Please bring the Wisepill device with you to every clinic visit. You will have to return the Wisepill after the study is complete.

You will be expected to attend on your appointment date or to contact the study nurse and change the date if you cannot.

Risks and benefits: There is a small risk that people will identify you as HIV-positive through the use of the Wisepill, although previous studies have shown that this is rarely the case and that people using it quite like the look of the pill box.

The risk of having extra blood draws is small, perhaps bruising or pain where the needle went in. Some people find having blood drawn very unpleasant.

There may be benefits to you in that being on the study provides extra support to you in the first year of your treatment and so helps you to take your ART better.

Reimbursement: You will be reimbursed R20 for the extra time you have to spend at the clinic (for the questionnaires) and the extra blood that has to be drawn. This reimbursement will occur only on the 5 scheduled study visits outlined above. You will be reimbursed R150 for the final study visit, which is an extra visit. You should not incur any other expenses during the study as you would be attending Hannan for ART care in any case.

Confidentiality: Your name and address will never leave Hannan. You will be identified only by a code and a number. All staff sign confidentiality agreements and will never reveal your status to any other person.

At times someone from outside (e.g. the Ethics Committee) may want to review the files we use for the study. This will also be done in complete confidence.

Contact details for the study team:

Principal Investigator: Dr Catherine Orrell, Desmond Tutu HIV Centre, IIDMM, University of Cape Town, Faculty of Health Science. Phone 021 650 6958.

Study coordinator: Sr. Heidi Freislich, Hannan Crusaid treatment Centre, NY 3, Gugulethu. Phone 021 633 5963.

This study will be completed according to the International Declaration of Helsinki and meet Good Clinical Practice principles. This study has been approved by the University of Cape Town Research Ethics Committee.

Complaints may be directed to the Chairperson of Faculty of Health Sciences, Human Research Ethics Committee, at the University of Cape Town, Prof Marc Blockman at 021 406 6338.

Thank you for taking the time to read this information. If you agree to participate, please sign below. If new information becomes available during the study we will update this form and give you a new one to sign.

I have read the information about the TAP study and I have had a chance to ask questions.

I agree to participate in the study and know I may withdraw at any time.

_____	_____	_____
Patients' full name and surname	Signature	Date

_____	_____	_____
Witness's full name and surname	Signature	Date
(If patient is illiterate)		or N/A <input type="checkbox"/>

_____	_____	_____
Study staff's full name and surname	Signature	Date

Appendix 2: CAGE questionnaire

Date:	dd - mmm - yyyy	Patient number:	ZZ 9999
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CAGE questionnaire.

Ask the following questions:

Have you ever felt you needed to Cut down on your drinking? Yes ☐ No ☐

Have people Annoyed you by criticizing your drinking? Yes ☐ No ☐

Have you ever felt Guilty about drinking? Yes ☐ No ☐

Have you ever felt you needed a drink first thing in the morning (Eye-opener) to steady your nerves or to get rid of a hangover? Yes ☐ No ☐

Each YES = 1 point. Write SCORE (1-4) here and on questionnaire CRF: SCORE: _____

[Two "yes" responses indicate that the possibility of alcoholism should be investigated further → place copy of this form in Hannan folder.]

Appendix 3: HADS questionnaire.

Hospital Anxiety and Depression Scale: Scoring Sheet

	Yes, definitely	Yes, some- times	No, not much	No, not at all
1. I wake early and then sleep badly for the rest of the night.	3	2	1	0
2. I get very frightened or have panic feelings for apparently no reason at all.	3	2	1	0
3. I feel miserable and sad.	3	2	1	0
4. I feel anxious when I go out of the house on my own.	3	2	1	0
5. I have lost interest in things.	3	2	1	0
6. I get palpitations, or sensations of 'butterflies' in my stomach or chest.	3	2	1	0
7. I have a good appetite.	0	1	2	3
8. I feel scared or frightened.	3	2	1	0
9. I feel life is not worth living.	3	2	1	0
10. I still enjoy the things I used to.	0	1	2	3
11. I am restless and can't keep still.	3	2	1	0
12. I am more irritable than usual.	3	2	1	0
13. I feel as if I have slowed down.	3	2	1	0
14. Worrying thoughts constantly go through my mind.	3	2	1	0

Add the scores for anxiety and depression:

Anxiety 2, 4, 6, 8, 11, 12, 14: Total _____

Depression 1, 3, 5, 7, 9, 10, 13 Total _____

GRADING: 0 - 7 = Non-case 8 – 10 = Borderline case 11+ = Case

Appendix 2: University of Cape Town Research Ethics Committee approval letters.

1. Observational cohorts

UNIVERSITY OF CAPE TOWN UNIVERSITEIT VAN KAAPSTAD		HUMAN RESEARCH ETHICS COMMITTEE - 9 JAN 2015		FACULTY OF HEALTH SCIENCES Human Research Ethics Committee	
FHS016: Annual Progress Report/ Renewal					
HREC office use only (FWA00001637; IRB00001938)					
This serves as notification of annual approval, including any documentation described below.					
<input checked="" type="checkbox"/> Approved	Annual progress report	Approved until/next renewal date	30.1.2016		
<input type="checkbox"/> Not approved	See attached comments				
Signature Chairperson of the HREC		Signed by candidate		Date Signed 11/1/2015	
Comments to PI from the HREC					
Thank you for your letter 6th Jan 2015					
Principal Investigator to complete the following:					
1. Protocol information					
Date form submitted	06 th January 2015				
HREC REF Number	379/2002	Current Ethics Approval was granted until	22 nd Jan 2015		
Protocol title	Data collection at the Hannan Crusaid ART treatment Centre in Guguletu and at the Masiphumelele ART roll-out site				
Protocol number (if applicable)	n/a				
Are there any sub-studies linked to this study?				<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
If yes, could you please provide the HREC Ref's for all sub-studies? Note: A separate FHS016 must be submitted for each sub-study. There are no sub-studies.					
Principal Investigator	Dr Catherine Orrell, Prof Robin Wood				
Department / Office Internal Mail Address	Desmond Tutu HIV Foundation, N1.21.5 Werner Beit North, IDM, Faculty of Health Science				
1.1 Does this protocol receive US Federal funding?				<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
1.2 If the study receives US Federal Funding, does the annual report require full committee approval?				<input type="checkbox"/> Yes	<input type="checkbox"/> No

2. Randomised controlled study (TAP study) – initial, annual renewals and closure

UNIVERSITY OF CAPE TOWN



Health Sciences Faculty
Human Research Ethics Committee
Room E52-24 Groote Schuur Hospital Old Main Building
Observatory 7925
Telephone [021] 406 6338 • Facsimile [021] 406 6411
e-mail: shuretta.thomas@uct.ac.za

24 May 2012

HREC REF: 158/2012

Dr C Orrell
Desmond Tutu, HIV Foundation
IIDMM
Medical School

Dear Dr Orrell

PROJECT TITLE: A RANDOMISED CONTROLLED TRIAL TO EXPLORE ADHERENCE-FAILURE RELATIONSHIPS IN A SOUTH AFRICAN ANTIRETROVIRAL DELIVERY SITE USING AN ELECTRONIC ADHERENCE DEVICE AND SPARSE PHARMACOKINETIC SAMPLING.

Thank you for responding to the issues raised by the Faculty of Health Sciences Human Research Ethics Committee in your letter dated 18th May 2012.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study provided the MCC Approval is granted.

Approval is granted for one year till the 30th May 2013

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.

(Forms can be found on our website: www.health.uct.ac.za/research/humanethics/forms)

The following documentation is noted and approved:

1. TAP Clinical Protocol version 1.1 dated 18 May 2012
2. Research Consent Form
3. Study Synopsis
4. TAP Study patient information sheet version 1.1 dated 18 May 2012
5. Budget

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the HREC. REF in all your correspondence.

Yours sincerely

Signed by candidate

PROFESSOR M BLOCKMAN
CHAIRPERSON, HSF HUMAN ETHICS
Federal Wide Assurance Number: FWA00001637.

s.thomas

HREC Ref 158/2012 – 24 May 2012



UNIVERSITY OF CAPE TOWN
UNIVERSITEIT KAPSTADT - UNIVERSITEIT KAPSTADT

HUMAN RESEARCH
ETHICS COMMITTEE

15 MAY 2013

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS016: Annual Progress Report / Renewal

UNIVERSITY OF CAPE TOWN

HREC office use only (FWA00001637; IRB00001938)			
This serves as notification of annual approval, including any documentation described below.			
<input checked="" type="checkbox"/> Approved	Annual progress report	Approved until next renewal date	20/5/2014
<input type="checkbox"/> Not approved	See attached comments		
Signature Chairperson of the HREC	Signed by candidate	Date Signed	15/5/2013

Principal Investigator to complete the following:

1. Protocol information

Date form submitted	13 May 2013		
HREC REF Number	158/2012	Current Ethics Approval was granted until	30 th May 2013
Protocol title	A randomised controlled Trial to explore Adherence-failure relationships in a South African antiretroviral delivery site using an electronic adherence device and sparse Pharmacokinetic sampling. (TAP study)		
Protocol number (if applicable)	n/a		
Principal Investigator	Dr Catherine Orrell		
Department / Office Internal Mail Address	Desmond Tutu HIV Centre, Room N1.21.5 Werner-Beit Building North, IIDMM, UCT Faculty of Health Sciences.		

1.1 Does this protocol receive US Federal funding?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
1.2 Has sponsorship of this study changed? If yes, please attach a revised summary of the budget.	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No

2. List of documentation

TAP protocol – 28Jan2013 (version 2.1).
ADULT information leaflet and consent form for the TAP study-28Jan13 (version 1.2).
PARENT information leaflet and consent form for the TAP study-28Jan13 (version 1.2).
CHILD information leaflet and consent form for the TAP study-28Jan13 (version 1.2).
Genetic testing consent for TAP study – 18May12 (version 1.0)
Wisepill device-acceptability qu-16Jan13 (version 2.0)



13 MAY 2014

FHS016: Annual Progress Report / Renewal

HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

HREC office use only (FWA00001637; IRB00001938)			
This serves as notification of annual approval, including any documentation described below.			
<input checked="" type="checkbox"/> Approved	Annual progress report	Approved until/next renewal date	30.5.2015
<input type="checkbox"/> Not approved	See attached comments		
Signature Chairperson of the HREC	Signed by candidate	Date Signed	13/5/2014

Principal Investigator to complete the following:

1. Protocol information

Date form submitted	12 May 2014		
HREC REF Number	158/2012	Current Ethics Approval was granted until	30 th May 2014
Protocol title	A randomised controlled Trial to explore Adherence-failure relationships in a South African antiretroviral delivery site using an electronic adherence device and sparse Pharmacokinetic sampling. (TAP study)		
Protocol number (if applicable)	n/a		
Principal Investigator	Dr Catherine Orrell		
Department / Office Internal Mail Address	Desmond Tutu HIV Centre, Room N1.21.5 Werner-Beit Building North, IIDMM, UCT Faculty of Health Sciences.		

1.1 Does this protocol receive US Federal funding?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
1.2 Has sponsorship of this study changed? If yes, please attach a revised summary of the budget.	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No

2. List of documentation

<p>TAP protocol – 28Jan2013 (version 2.1).</p> <p>ADULT information leaflet and consent form for the TAP study-28Jan13 (version 1.2).</p> <p>PARENT information leaflet and consent form for the TAP study-28Jan13 (version 1.2).</p> <p>CHILD information leaflet and consent form for the TAP study-28Jan13 (version 1.2).</p> <p>Genetic testing consent for TAP study - 18May12 (version1.0).</p> <p>Wisepill device-acceptability qu-16Jan13 (version 2.0)</p> <p>Recent Life Events Questionnaire -26Jun13 (Version 1)</p>
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3. Protocol status (tick ✓)



UNIVERSITY OF CAPE TOWN
YUNIBESITHI YASENAPA • UNIVERSITEIT VAN KAAPSTAD

RESEARCH ETHICS COMMITTEE

2015 -07- 15

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee



HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

Form FHS010: Study Closure Report

HREC office use only (FWA00001637; IRB00001938)			
Noted and filed. This serves as acknowledgement that this study is closed.			
<input checked="" type="checkbox"/> Approved	Study closure report		
<input type="checkbox"/> Not Approved	Study closure report		
Chairperson of the HREC signature		Date	17/7/15

1. Principal Investigator to complete the following:

Date (when submitting this form)	14 Jul 2015
HREC REF Number	158/2012
Protocol Title	A randomised controlled Trial to explore Adherence-failure relationships in a South African antiretroviral delivery site using an electronic adherence device and sparse Pharmacokinetic sampling.
Protocol number (if applicable)	
Principal Investigator	Catherine Orrell
Department / Office Internal Mail Address	Desmond Tutu HIV Centre, IIDMM, Wernher Beit North

2. Please confirm (tick ✓)

This study is closed to enrollment	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
Participants have completed all research-related interventions	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
Participants have completed all research-related follow-up	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
Data analysis is complete	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
Your sponsored protocol is closed	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No

Appendix 3: Adherence Experts Consultation Summary Report.

This summary document attached here is the initial version compiled by Dr Jessica Haberer and is NOT the final version, which is being commented on by other of the meeting attendees, before being drafted for publication.

Adherence Experts Consultation Summary Report Regarding Consultation Presentations and Discussion: Vancouver, July 18, 2015

Background

In advance of the consultation, participants were asked to submit “one or two of the most significant abstracts or program descriptions in your area of expertise.” These materials were then compiled and disseminated by the Co-Chairs in advance of the consultation. In total, over 300 pages of materials were compiled, disseminated, and reviewed regarding the following categories of promising ART adherence interventions: (i) individual counseling interventions, (ii) peer and family support interventions, (iii) healthcare system/community interventions, (iv) electronic interventions, (v) behavioral economics/economic empowerment, and (vi) other/summary information. These materials are available on request.

Presenters were asked to make a brief presentation (5-10 minutes) describing evidence-based interventions and their impact, focusing specifically on the relative scalability of the intervention – whether the intervention had been tested at scale, what were barriers to scale up, and what would be necessary to support broad scale-up. Following each presentation, the Co-Chairs facilitated open discussion. The last two hours of the consultation were devoted to developing consensus recommendations regarding those interventions that were, in the opinion of participants, materially and positively impactful on adherence and immediately scalable.

Individual Counseling and Peer/Family Support Interventions (Discussion Led By Rivet Amico, Robert Remien, and Jean Nachega)

Counseling for adherence is an exchange of information about medication and health, and is most effective when implemented simultaneously with other interventions – such as family engagement, cognitive education, or peer support. Counseling can take different forms. Cognitive behavioral therapy (CBT) focuses on the “think-feel-behave” cycle and requires several sessions (typically with a trained counselor). CBT helps influence adherence behavior through self-reflection and development of coping tools. Another form of counseling, motivational interviewing (MI), focuses on decision-making and motivation. Other forms of counseling include electronic dose monitoring-driven counseling, multi-media-supported counseling, narrative stories, music, and theater. Several attendees noted that counseling that utilizes storytelling helps address disclosure, bereavement, depression, social support,

and similar barriers to care. These engagement interventions, it was noted, are particularly effective with youth.

There is strong evidence that counseling is highly influenced by the counselor and is most effective when done by peers. However, peer support based interventions are difficult to standardize, and some patients lack an existing support network to leverage. Given stigma and related issues, it is important that peers be selected by the patient and not provided or otherwise imposed on the patient. It was noted that a benefit of the use of multimedia and other supporting technologies is that it can standardize, streamline, and improve the overall quality of counseling. Finally, all such counseling is more effective if stigma is not an issue and if the patient's family can be engaged and involved in such counseling and patient support.

Although these forms of enhanced counseling and support have been proven to be effective, particularly when combined with additional interventions, they have not been scaled up to date. This is due in large part to the facts that (i) acceptability of enhanced counseling is based on the quality of counselor care and as yet counselor quality is often poor, and (ii) mechanisms to automate or scale the peer selection and peer counseling processes are embryonic at this point. Importantly, virtually every clinic and every provider is doing some form of counseling – however modest, however ad hoc. Thus, there is an immediate and existing opportunity to improve overall medication adherence by improving, standardizing, and automating this existing counseling and working toward incorporating therein some of these proven-effective enhanced and peer-based counseling techniques.

Healthcare System/Community Interventions (Discussions Led by Elvin Geng and Sherri Weiser)

Health systems are overburdened by a high patient load and limited resources, and the burden is continuously increasing. Healthcare systems have a direct effect on patient adherence and follow-up (e.g., long lines at clinics or extended travel to clinics can lead to delayed refill and resultant treatment interruptions), and patient interactions with health care workers can positively or negatively influence adherence and retention. Thus, improvements in these logistical and human interactions elements of health care delivery can be highly impactful on initiation, implementation, and persistence.

Pilot programs have shown that approaches that streamline and reduce the patient burden with respect to medication refill are well received and impactful. Two approaches were discussed. In the first, patients perceived to have good adherence (e.g., per viral load suppression) are permitted to obtain their medications via an “adherence club.” These clubs may provide some adherence counseling and peer support, as well as enable a “fast track” refill mechanisms. In the second, patients are placed in groups of approximately six patients and one member of the group (rotating each month) is permitted to obtain refills for all of the patients in his or her group. These approaches decrease the patient burden on health facilities, reduce transportation costs and waiting times for patients, help overcome structural barriers, reduce treatment fatigue and loss to follow up, increase disclosure and treatment education, and help patients develop necessary social ties.

Electronic Interventions (Discussion Led by Rich Lester and Catherine Orrel)

Electronic interventions are an additional resource for patients to connect with their healthcare systems, and can help improve adherence in resource-limited settings. Electronic dose monitoring (EDM) provides critical data on adherence patterns (thus permitting the early and accurate identification of those struggling with adherence) and can be combined with social network–based interventions and delivery of counseling. Evidence suggests that counseling informed and enabled by detailed dosing histories is a highly effective adherence intervention. Moreover, it was noted that (i) adherence monitoring through electronic-based interventions may be cost-effective because it reduces human workload and is generally well liked by patients (Wisepill in particular), and (ii) that EDM can also help identify which patients might need expensive HIV RNA testing, and identify virologic failure before it becomes clinically significant.

Another electronic intervention worth noting is SMS, particularly the weekly SMS system developed by Wel-Tel. Wel-Tel’s SMS intervention uses SMS to connect with and assess patient adherence via SMS-based self-reporting. It uses SMS messages that ask patients “How are you?” (“Mambo?” in Swahili). These discrete messages serve as points of contact between providers and patients, as well as reminder messages for drug adherence. Because HIV and/or medications are not mentioned, accidental disclosure on shared devices is unlikely. Studies have found that this type of engagement and support benefit is more effective than simple reminders, and the program is cost-effective and scalable. Studies have also shown that message content has a limited effect on adherence, but timing and frequency of the message are crucial to success.

There was also discussion of using SMS approaches, such as Wel-Tel, for adherence monitoring, both identifying poor adherers generally and compiling more detailed dosing histories. However, self-reporting is not always reliable, and Wel-Tel does not address how best to reach patients who are unwilling to engage in care and report their health status. Effectiveness may also vary widely as follow-up care is diverse and program-based. Nevertheless, SMS reminders and approaches like Wel-Tel are inexpensive in relative terms and scalable, and represent an interesting and potentially important part of a comprehensive adherence program.

Interventions Related to Behavioral Economics/Economic Empowerment (Discussion Led by Omar Gallaraga and Alex Tsai)

Behavioral economics may help HIV research by determining and addressing economic barriers to health and by evaluating the impact of incentives on medication adherence. Social and economic factors are huge influences to care and are accurate indicators of attrition. Most of the current behavioral economic research focuses on the interface between poverty and stigma, because HIV-positive individuals are less able to contribute to their communities and are targeted for exclusion. Programs that promote contributions to society by HIV-positive individuals can help address the stigma-exclusion cycle. Microfinance and other economic programs can lead to social integration, increased food security, community reciprocity, and reduced stigma. Livelihood programs, such as lease-to-own and savings groups, help provide empowerment to persons living with HIV and their families.

Current incentive practices vary widely by type, amount, length of time, and whether incentives are conditional or not. Most economists prefer unconditional cash transfers, but “loan plus training” and “in-kind loan plus training” are also used as incentive models. Non-cash incentives have proven effective with youth (e.g., a can of tuna) in establishing behaviors that lead to engagement of care. Yet economists doubt whether these loan programs are sustainable without a steady influx of resources from investors, and whether they work in low-income environments. Incentives can also motivate patients to misreport their circumstances to qualify for studies and/or increase their cash incentive. Incentives may also shift the balance of power in a family environment and lead to peer and family pressures.

Conclusions and Consensus Recommendations (Discussion Facilitated by Jessica Haberer and David Bangsberg)

At the outset, it is important to note that the group was unanimous in its view that adherence is and remains a major obstacle to advancing toward the goal of ending AIDS. The group also agreed that statistics regarding “average adherence” are misleading, particularly when based on self-reporting, pill counts and other methods agreed to have strong positive bias. Additionally, a large number of non-adherent patients are ignored by adherence interventions because they are not identified in the first place. Most adherence interventions understandably focus on ongoing treatment. While it is key to establish positive adherence behaviors early, it is also necessary to engage patients in care to improve adherence long-term, as nearly all individuals will struggle with adherence at some point during their lifetimes. Most study designs, however, look at the short-term (i.e., one year or less) and miss important effects over time. It is equally important to track adherence before patients begin to miss clinic visits and before viral load changes become apparent.

The group was strongly of the view that it is important to move toward differentiated care by separating the “doers from the non-doers,” to quote Linda Gail Bekker (Desmond Tutu HIV Foundation). The group acknowledged and agreed that, particularly as HIV treatment targets are expanded, it is increasingly important and positively impactful to identify those patients who need more help with adherence and to be able to allocate relatively more resources toward them. This assessment needs to take place on a continuing basis, given the length of ARV therapy and the fact that patterns of adherence and poor adherence change over time. There is a need for increased monitoring and support for high-risk populations (e.g., youth, elderly, pregnant/post-partum women, individuals with chronic health conditions, lifestyle risks); however, those criteria alone shouldn’t be used to identify people as “non-adherers”. While the group did not settle upon a particular methodology or technology to drive the identification of non-adherent patients, it was generally agreed that viral load testing alone is not the answer and that today’s best approaches (taking into consideration affordability, patient acceptance, and ability to generate detailed dosing histories) may well include interactive SMS and electronic dose monitoring. The group discussed both “funnel” and “menu” approaches. With a funnel approach, the largest possible number of individuals would be screened for non-adherence. Those identified as such (including those who never initiate care) would receive one standard intervention strategy. The intensity of interventions would then increase for the likely decreasing number

of individuals who continue to have adherence challenges. The first intervention should be the most appealing, so that patients do not stop adherence to gain benefits of later funnel steps (ex: personalized care, incentives, etc.). With the menu approach, a number of intervention options could be presented to individuals, allowing them to choose their intervention strategy. Menus could be altered for specific populations (e.g., adolescents engaging in mHealth, patients with depression in counseling, socioeconomic barriers in “adherence clubs”, etc.).

There was also broad agreement that in recent years more has been done at the individual clinic level to address poor adherence – both avoiding poor adherence and intervening to correct poor adherence. At virtually every clinic, some form of counseling or educational support is provided to patients – explaining why adherence is important and offering encouragement as well as some basic techniques to use to remain adherent. However, current efforts are less effective and less efficient than they might otherwise be because these efforts (i) are applied on a “one size fits all” basis, (ii) are not informed or supported by accurate or detailed adherence data, and (iii) do not address or ameliorate the inherent challenges in the current clinic-based approach to patient management (e.g., long waiting times, travel, stigma).

In terms of specific interventions, those that received the most support and/or favorable response from the group were as follows:

- Tools to standardize, automate, or enhance individual patient counseling. These include laptop or tablet-based tools to provide more interactive education and counseling as well as some approaches that use picture books and similar education and counseling tools;
- Interventions that address some of the clinic setting-specific issues that negatively affect adherence. Particularly interesting to the group were “adherence clubs” or other mechanisms to reduce the burden associated with medication refill. However, it was noted that it is essential that some reliable monitoring mechanism be used to ensure this “fast track” approach is used only with patients who are good adherers;
- Interventions that involve peer and family support also were viewed as interesting and impactful. However, there was a belief that these interventions were most appropriate as a response to demonstrated poor adherence, as opposed to generally available for all patients upon treatment initiation;
- Although it was not discussed at length, there was general acknowledgement that there is potential in creating, maintaining, and leveraging pharmacy refill data. In many clinics, refill data is fairly robust; however, refill data is rarely shared with clinicians or otherwise used to identify poor adherers or those at risk of becoming poor adherers;
- There was strong interest in the potential of weekly SMS as a patient reminder and as a way to strengthen patient-clinic connection and related emotional and other support. This approach is inexpensive and in several studies has been shown to

positively affect adherence. There was discussion but not agreement as to whether SMS is an effective way of identifying poor or potentially poor adherers as there were concerns about the accuracy of patient self-reporting and also about patient burden and fatigue over time. Nevertheless, SMS was broadly viewed as technology with potential and technology that is scalable today;

- Finally, there was support for the use of electronic dose monitoring to both generate the sort of detailed dosing histories that allow the identification of poor adherers and also to inform and support other interventions such as peer or family support or more intensive counseling. A number of attendees had positive experience with electronic dose monitoring and there was a general belief that at a lower per unit price point electronic dose monitor would be scalable.